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Biological Consequences of Disturbed Sleep: Important Mediators of Health?

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Abstract

There is an extensive literature regarding the immunological and endocrinological consequences of illness, stress, and psychopathology. Yet only a modest literature is available regarding the potential unfavorable effects of chronic sleep loss/disruption on immune and endocrine pathways or on various aspects of health. Given that humans spend approximately 1/3 of their lives asleep, it seems pertinent to evaluate this necessary yet understudied behavior. The evidence overwhelmingly indicates that “excessive” sleep disruption or poor sleep quality/continuity may subsequently increase risk for adverse health outcomes, as well as mortality. This is thought to occur through dysregulation of biological pathways. While our information addressing the immunological or endocrinological consequences of poor sleep is mounting, the majority of evidence stems from epidemiologic and cross-sectional studies. The immune and endocrine systems are dynamic and constantly in flux. Thus, the methodologies and study designs used to understand how sleep affects these systems needs to be as dynamic. Experimental manipulations and longitudinal evaluations are needed to effectively understand sleep as a risk factor for health. Thus, this paper is a primer in which to highlight the immunological and endocrinological consequences of disrupted or disturbed sleep as well as describe how these relationships may impact overall health. It is also meant to spark an interest for future evaluations of how the behavior of sleep is relevant to health.

Keywords

sleep; immune; health; endocrine

Sleep Physiology

Sleep has received the attention of philosophers, scientists, psychiatrists, and artists for centuries. Once thought to be a passive and inactive state, sleep is now viewed as an active process in which various metabolic processes, tissue restoration, memory consolidation, and homeostatic balance is maintained (Adam, K., 1980; Alvarez, G. G. & Ayas, N. T., 2004; Ancoli-Israel, S., 2006; Benca, R. & Quinlan, J., 1997). The notion that sleep is a period of unconsciousness with little utility is shattered by the fact that humans spend 1/3 of each day asleep during which both the brain and body are particularly active. While it is established as an important homeostatic process and physiologic behavior, there are still many unanswered questions as to why we sleep, how much sleep is actually needed, and the extent of the ramifications when we do not get enough sleep. We know, for example, that experimental sleep deprivation or restriction protocols conducted in healthy young adults lead to profound changes in central and peripheral physiology as well as functional changes

in cognition, affect, performance and behavior (Irwin, M. R., Wang, M., Campomayor, C. O., Collado-Hidalgo, A., & Cole, S., 2006; Lim, J. & Dinges, D. F., 2008; Sari, I., Davutoglu, V., Ozbala, B., Ozer, O., Baltaci, Y., Yavuz, S., & Aksoy, M. 2008; Stricker, J. L., Brown, G. G., Wetherell, L. A., & Drummond, S. P., 2006; Redwine, L., Hauger, R. L., Gillin, J. C., & Irwin, M., 2000; Spiegel, K., Leproult, R., & Van Cauter, E., 1999; Spiegel, K., Sheridan, J. F., & Van Cauter, E., 2002; Spiegel, K., Tasali, E., Penev, P., & Van Cauter, E., 2004; Vgontzas, A. N., Zoumakis, E., Bixler, E. O., Lin, H. M., Follett, H., Kales, A., & Chrousos, G. P., 2004). While there is still much to learn about sleep and its functions, one would be hard pressed to ignore the importance of a behavioral state that incorporates such a large proportion of each 24-hour period and the potential negative consequences when an insufficient amount is achieved.

Sleep, as we currently understand it, is a complex biobehavioral process that can be characterized along multiple dimensions (Hall M, Okun ML, Atwood CW, Buysse DJ, & Strollo PJ, 2008; Hall M, 2010). Sleep changes across the lifespan, from infancy through old age, and may, additionally be modulated by sex, race/ethnicity and mental or physical health conditions (Hall, M. H., Matthews, K. A., Kravitz, H. M., Gold, E. B., Buysse, D. J., Bromberger, J. T., Owens, J. F., & Sowers, M., 2009; Carrier, J., Land, S., Buysse, D. J., Kupfer, D. J., & Monk, T. H., 2001; Carskadon, M. & Dement, W. C., 2005; Ohayon, M. M., Carskadon, M. A., Guilleminault, C., & Vitiello, M. V., 2004). As a behavior, sleep is a reversible state of perceptual disengagement from and unresponsiveness to the environment (Carskadon, M. & Dement, W. C., 2005). It is typically accompanied by postural recumbence, behavioral quiescence, closed eyes, and differential breathing (Carskadon, M. & Dement, W. C., 2005). Within sleep, there are two physiological states: non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. These states are defined using physiological measurements including brain activity via the electroencephalogram (EEG), muscle tone via the electromyogram (EMG), and eye movements via the electroculogram (EOG) (Carskadon, M. & Dement, W. C., 2005) (Fuller, P. M., Gooley, J. J., & Saper, C. B., 2006). NREM sleep is usually associated with limited or fragmented mental activity. It is presently subdivided into three stages: Stage 1 (high frequency, low amplitude wave forms) is characterized by a low arousal threshold and is very brief in duration; Stage 2 (similar to Stage 1 but with sleep spindles) is characterized by a higher arousal threshold and constitutes about half of sleep; and SWS (Stages 3 & 4; high-voltage slow wave activity) dominates the first third of the night and constitutes about 20% of sleep. REM sleep, on the other hand, is marked by mixed high-frequency, low-amplitude EEG waves, muscle atonia, and episodic bursts of rapid eye movements. REM sleep is about 20-25% of sleep with REM periods becoming longer as the night progresses (Carskadon, M. & Dement, W. C., 2005).

Why is Sleep So Important?

Restorative Function of Sleep

The requirement for sleep is a basic physiological need and has similar homeostatic properties to hunger or thirst such that sleep reverses sleepiness (Roehrs T, Carskadon MA, Dement WC, & Roth T, 2005). There is an intrinsic circadian (24-hour) sleep-wake cycle that parallels the daily rhythm of many physiological processes, including the endocrine and immune systems (Akerstedt, T. & Nilsson, P. M., 2003; Roehrs T, Carskadon MA, Dement WC, & Roth T, 2005). The importance of sufficient sleep to health outcomes is highlighted by the mounting evidence that disturbed sleep (short/long sleep duration, and poor sleep quality or continuity) is associated with a host of adverse health outcomes ranging from the common cold (Cohen, S., Doyle, W. J., Alper, C. M., Janicki-Deverts, D., & Turner, R. B., 2009) to postpartum depression (Okun, M. L., Hanusa, B. H., Hall, M., & Wisner, K. L., 2009) to cardiovascular disease (Gangwisch, J. E. et al., 2006; Meisinger, C., Heier, M.,

Lowel, H., Schneider, A., & Doring, A., 2007). For this reason, the impact of sleep loss/disturbance reaches beyond the immediate realm of just making an individual sleepy; it can impact the entire biological entity either directly or indirectly, due to the multiple brain regions, immune and endocrine factors, and various neurotransmitters involved in sleep regulation (Benca, R. & Quintas, J., 1997).

Sleep and Immune Function

The immune system is important to consider when discussing the consequences of poor or disrupted sleep. It is our primary protection against illness and disease, and a constant surveyor of the internal environment. The immune system and its products are important mediators of both current and future health outcomes. An imbalance in their production can compromise the efficiency of the system's immediate and long-term ability to ward off disease and maintain health. A consistent array of empirical data supports a role for adequate sleep in efficient immune functioning. For instance, increased peripheral leukocytes (Born, J., Lange, T., Hansen, K., Molle, M., & Fehm, H. L., 1997; Dinges, D.F., Douglas, S.D., Zaugg, L., Campbell, D.E., McMann, J.M., Whitehouse, W.G., Orne, E.C., Kapoor, S.C., Icaza, E., & Orne, M.T. 1994; Faraut, B., Boudjeltia, K.Z., Dyzma, M., Rousseau, A., David, E., Stenuit, P., Franck, T., Van Antwerpen P., Vanhaeverbeek, M., & Kerkhofs, M., 2011; Ruiz, F.S., Andersen, M.L., Martins, R.C., Zager, A., Lopes, J.D., & Tufik, S., 2010) and elevated C-reactive protein and inflammatory cytokines (Dimitrov, S., Lange, T., Tiekens, S., Fehm, H. L., & Born, J., 2004; Frey, D. J., Fleschner, M., & Wright, K. P., Jr., 2007; Irwin, M. R., Wang, M., Campomayor, C. O., Collado-Hidalgo, A., & Cole, S., 2006; Vgontzas, A. N. et al., 2004) are observed following a sleep restriction protocol. Highlighting the fact that sleep is critical for health is clear from studies showing marked improvements (e.g. reductions) in cytokine concentrations after the introduction of a nap or recovery sleep (Faraut, B. et al., 2011; Ruiz, F. S. et al., 2010; Vgontzas, A.N., Pejovic, S., Zoumakis, E., Lin, H.M., Bixler, E.O., Basta, M., Fang, J., Sarrigiannidis, A., & Chrousos, G.P., 2007).

Investigators have most commonly evaluated aggregate measures of sleep. In other words, total sleep duration, sleep continuity or sleep quality is assessed across a period of time. Recently, however, there has been a growing interest in understanding the impact of variability in sleep (Buysse, D.J., Cheng, Y., Germain, A., Moul, D.E., Franzen, P.L., Fletcher, M., & Monk, T.H., 2010; Knutson, K. L., Rathouz, P. J., Yan, L. L., Liu, K., & Lauderdale, D. S., 2007; Mezick, E.J., Matthews, K.A., Hall, M., Kamarck, T.W., Buysse, D.J., Owens, J.F., & Reis, S.E. 2009). Recently, Okun et al reported that variability in bed and wake times were linked with increased circulating cytokines among elderly good sleepers (Okun, M.L., Reynolds, C.F., III, Buysse, D.J., Monk, T.H., Mazumdar, S., Begley, A., & Hall, M., 2010). The authors suggest that individuals who have significant variability in their bed and wake times may be at increased risk for adverse health outcomes via activation of inflammatory pathways. However, these authors did not show that all indices of disrupted sleep negatively impact immune correlates. A similar conclusion was reached in another recent study that found no significant impact of shift work (a chronic circadian disruptor) on IL-6 or TNF- α concentrations (van Mark A., Weiler, S.W., Schroder, M., Otto, A., Jauch-Chara, K., Groneberg, D.A., Spallek, M., Kessel, R., & Kalsdorf, B., 2010). While both these studies are exploring novel relationships, it is unclear as to whether the diurnal rhythm of these cytokines is minimally affected by changes in sleep times when only one blood sample is available. Vgontzas and colleagues emphasize the importance of evaluating serial measures of immune function with a study that showed how mild sleep restriction over the course of a week increased IL-6 levels over the 24-hour period while the diurnal rhythm remained intact (Vgontzas, A. N. et al., 2004). Additional investigation of the dynamics between sleep variables and immune changes is needed in order to effectively intervene and improve health.

The relationship between sleep and the immune system is not one-way. There is ample evidence of a bi-directional association and the presence of several feed-forward processes between sleep and the immune system (Benca, R. & Quinlan, J., 1997; Lange, T., Dimitrov, S., & Born, J., 2010; Opp, M. R., 2006; Opp, M. R., 2009). As described earlier, sleep, which can be considered a physiological stressor when it is disrupted (McEwen, B. S., 2006), can activate immune processes. It is likely through chronic, rather than acute immune activation, that sleep contributes to disease. This is evidenced by some epidemiologic data showing that poor sleep is associated with higher levels of inflammation years later (Liukkonen, T., Rasanen, P., Ruokonen, A., Laitinen, J., Jokelainen, J., Leinonen, M., Meyer-Rochow, V. B., & Timonen, M., 2007; McDade, T. W., Hawkey, L. C., & Cacioppo, J. T., 2006). Yet, this is purely correlational, not causal. The bulk of causal evidence is derived from short-term studies that show sleep deprivation, disruption or poor quality can initiate aberrant production of, as well as delays in nocturnal release of sleep-associated cytokines, IL-1, IL-6 and TNF- α , with subsequent recuperation of normal levels on recovery nights (Born, J., 1999; Frey, D. J., Fleshner, M., & Wright, K. P., Jr., 2007; Irwin, M., Clark, C., Kennedy, B., Christian, G. J., & Ziegler, M., 2003; Irwin, M., 2002; Okun, M. L. & Coussons-Read, M. E., 2007; Okun, M. L., Coussons-Read, M., & Hall, M., 2009; Opp, M., Born, J., & Irwin, M., 2006; Opp, M. R., 2006; Redwine, L., Hauger, R. L., Gillin, J. C., & Irwin, M., 2000; Savard, J., Laroche, L., Simard, S., Ivers, H., & Morin, C. M., 2003; Vgontzas, A. N., Zoumakis, M., Bixler, E. O., Lin, H. M., Prolo, P., Vela-Bueno, A., Kales, A., & Chrousos, G. P., 2003; Vgontzas, A. N., Zoumakis, M., Papanicolaou, D. A., Prolo, P., Vela-Bueno, A., Kales, A., & Chrousos, G. P., 2002). However, it is unclear whether these immune changes persist and/or have significant health consequences.

It is clear that immune activation induces somnolence as part of the host response to infection during the acute phase response by instructing monocytes/macrophages to produce cytokines such as IL-1, tumor necrosis factor (TNF)- α , and interferons (IFNs) (Akerstedt, T. & Nilsson, P. M., 2003; Born, J., 1999; Opp, M., Born, J., & Irwin, M., 2006). Experimental evidence shows that pro-inflammatory cytokines, such as TNF- α , IL-2, IFN- γ induce SWS, whereas anti-inflammatory cytokines, like IL-10 and IL-4 suppress SWS (Bryant, P. A., Trinder, J., & Curtis, N., 2004; Majde, J. A. & Krueger, J. M., 2005). The complex orchestration of cytokine production and balance by the immune system is not perfect. For instance, once the inflammatory cascade has been stimulated (i.e. via poor sleep), cytokines can amplify their own production via autocrine induction, resulting in an upregulation of the inflammatory process (Wilson, C. J., Finch, C. E., & Cohen, H. J., 2002) and further alterations in sleep (Haack, M., Sanchez, E., & Mullington, J. M., 2007; Pollmacher, T., Schuld, A., Kraus, T., Haack, M., Hinze-Selch, D., & Mullington, J., 2000). These feed-forward processes may have significant health consequences since amplified production of inflammatory cytokines may induce damage to otherwise healthy tissue (Kapsimalis, F., Basta, M., Varouchakis, G., Gourgoulis, K., Vgontzas, A., & Kryger, M., 2007; Opp, M., Born, J., & Irwin, M., 2006).

Our best understanding of this relationship comes from complimentary animal research which clearly shows that long-term sleep deprivation results in a proinflammatory state as indicated by elevated IL-1 β (Everson, C. A., 2005). Importantly, however, this systemic inflammation is associated with a decreased functional capacity to remove invading bacteria and toxins, suggesting impaired ability to defend against infection (Opp, M., Born, J., & Irwin, M., 2006). Long-term human studies are needed to confirm and extend these findings. In addition to evidence that sleep disruption results in systemic inflammation, it is widely accepted that circulating inflammatory mediators communicate with the central nervous system to induce sleep. Here, a large animal literature demonstrates that IL-1 β and TNF- α physiologically regulate normal sleep, while IL-6 modulates sleep during chronic pathology

(Hogan, D., Morrow, J. D., Smith, E. M., & Opp, M. R., 2003; Olivadoti, M. D. & Opp, M. R., 2008; Opp, M., Born, J., & Irwin, M., 2006).

Cytokines are the chemical messengers of the immune system (Ballieux, R. E., 1994). Although extremely important and often informative, the utility of measuring cytokines is limited by the fact that circulating cytokines can be produced by a variety of cells, including immune, muscle, adipose, and endothelial cells (Kapsimalis, F. et al., 2007; Kilroy, G.E., Foster, S.J., Wu, X., Ruiz, J., Sherwood, S., Heifetz, A., Ludlow, J.W., Stricker, D.M., Potiny, S., Green, P., Halvorsen, Y.D., Cheatham, B., Storms, R.W., & Gimble, J.M., 2007; Lappas, M., Permezel, M., & Rice, G. E., 2004). In response to this, a surge of studies have focused on the relationship between sleep disturbance and C-reactive protein (CRP). CRP is a marker of generalized inflammation. It has been identified as a reliable marker of disease risk with discernable cutoff values (Benderly, M., Haim, M., Boyko, V., Tanne, D., Behar, S., Matas, Z., Zimlichman, R., & Goldbourt, U., 2007). It has more recently been evaluated as a biological mediator between sleep and a host of illnesses including myocardial infarction, stroke, preeclampsia and other inflammatory diseases (Bautista, L. E., 2003; Benderly, M. et al., 2007; Cesari, M., Penninx, B.W., Newman, A.B., Kritchevsky, S.B., Nicklas, B.J., Sutton-Tyrrell, K., Tracy, R.P., Rubin, S.M., Harris, T.B., & Pahor, M., 2003; Diamanti-Kandarakis, E., Alexandraki, K., Piperi, C., Protogerou, A., Katsikis, I., Paterakis, T., Lekakis, J., & Panidis, D., 2006; Garcia, R.G., Celedon, J., Sierra-Laguado, J., Alarcon, M.A., Luengas, C., Silva, F., Arenas-Mantilla, M., & Lopez-Jaramillo, P., 2007; Meier-Ewert, H.K., Ridker, P.M., Rifai, N., Regan, M.M., Price, N.J., Dinges, D.F., & Mullington, J.M., 2004). While the evidence is mixed, self-report measures, including poor sleep quality and short sleep duration, appear to be correlated with higher CRP levels (Miller, M.A., Kandala, N.B., Kivimaki, M., Kumari, M., Brunner, E.J., Lowe, G.D., Marmot, M.G., & Cappuccio, F.P., 2009; Okun, M. L., Coussons-Read, M., & Hall, M., 2009; Patel, S.R., Zhu, X., Storfer-Isser, A., Mehra, R., Jenny, N.S., Tracy, R., & Redline, S., 2009).

Unlike other cytokines, CRP is a desirable marker to assay because it does not have a circadian rhythm. This ensures that concentrations are consistent regardless of time of day (Meier-Ewert, H.K., Ridker, P.M., Rifai, N., Price, N., Dinges, D.F., & Mullington, J.M., 2001). Also, unlike pro-inflammatory cytokines, CRP is produced only in the liver. Production is in response to circulating levels of inflammatory cytokines, such as IL-6 or TNF- α , thereby providing a more general reflection of systemic inflammation (Koenig, W., 2003; Meier-Ewert, H. K. et al., 2001). Taken together these studies support the hypothesis that disturbed sleep contributes to alterations in immune substrates and to an exaggerated inflammatory response. Further investigations are needed to understand the extent to which these immunological changes resulting from disturbed sleep affect the risk for poor health outcomes.

The clinical implications of persistent disturbed or insufficient sleep are emphasized in a small series of elegant studies in which sleep deprivation is shown to impair specific immune responses such as vaccination response (Lange, T., Perras, B., Fehm, H. L., & Born, J., 2003; Spiegel, K., Sheridan, J. F., & Van Cauter, E., 2002) and glucose metabolism and insulin sensitivity in healthy adults (Spiegel, K., Leproult, R., & Van Cauter, E., 1999; Spiegel, K., Tasali, E., Penev, P., & Van Cauter, E., 2004; Spiegel, K., Knutson, K., Leproult, R., Tasali, E., & Van Cauter, E., 2005). Additionally, a recent study showed that poor sleep efficiency, total sleep duration divided by time spent in bed, was associated with an increased risk of developing the common cold after experimental inoculation (Cohen, S., Doyle, W. J., Alper, C. M., Janicki-Deverts, D., & Turner, R. B., 2009). The consensus of these data suggest that cumulative sleep loss/disruption may induce an allostatic load resulting in general deviations of immune functions that can ultimately impair effective

immune responses and increase adverse health outcomes (Lange, T., Dimitrov, S., & Born, J., 2010; McEwen, B. S., 2006).

Insomnia and Immune Functioning: A Model

Experimental restriction of sleep and its consequences on the immune response is particularly illuminating. However, it is unethical to evaluate chronic sleep loss or disruption for an indefinite period of time. Thus, evaluating individuals with chronic insomnia offers investigators a unique opportunity to assess naturally occurring chronic sleep disruption/loss. A handful of investigations have shown immune dysregulation among people with insomnia. Savard and colleagues (2003) studied patients with and without insomnia to determine the effect that sleep disruption has on WBC subsets, NK cytotoxicity, and IL-1 β , IL-2, and IFN- γ production. They found that the patients with insomnia had lower counts of lymphocyte populations but no differences in WBC count, NK cell activity, or cytokine production. Sakami and colleagues (Sakami, S., Ishikawa, T., Kawakami, N., Haratani, T., Fukui, A., Kobayashi, F., Fujita, O., Araki, S., & Kawamura, N., 2002) found that men with insufficient sleep or difficulty initiating sleep had a shift toward Th2 dominance, indicated by higher levels of IL-4.

Another model in which to evaluate the effects of insomnia-like sleep disturbance on immunity is pregnancy. Many women experience sleep disturbance akin to insomnia throughout pregnancy, but particularly during the third trimester (Okun, M. L. & Coussons-Read, M. E., 2007). Okun and colleagues have shown that both circulating and stimulated levels of proinflammatory cytokines are higher among pregnant women with insomnia-like symptoms (long periods of wakefulness at night) compared to both pregnant women with shorter periods of wakefulness at night and non-pregnant women (Okun, M. L. & Coussons-Read, M. E., 2007; Okun, M. L., Hall, M., & Coussons-Read, M. E., 2007). By assessing immune function in pregnancy, a finite period of time when insomnia is often experienced, a better understanding of how immune function is altered and its consequences for health may become apparent.

In summary, there is a strong bi-directional relationship between sleep and the immune system. Many cytokines are involved in physiological sleep regulation and the expressions of some cytokines are greatly amplified by microbial challenge with excess cytokine production during infection inducing sleep responses. In addition to the exacerbation of sleep during infection, sleep disruption independently occurring during periods of stress, for example, are associated with dysregulation of the immune system. Understanding the dynamic relationship between sleep and the immune system will offer better comprehension of disease initiation as well as disease progression.

Sleep and endocrine function

The endocrine system is responsible for physiological integration of multiple organs by different actions of the endocrine axis (Andersen, M. L., Martins, P. J., D'Almeida, V., Bignotto, M., & Tufik, S., 2005). In concert with the immune system, the endocrine system is responsible for the body's stress systems and release of stress hormones necessary for adaptation and survival in an ever changing environment (Meerlo, P., Sgoifo, A., & Suchecki, D., 2008). Similar to the relationship between sleep and the immune system, elements of sleep and the endocrine system communicate bi-directionally (Steiger, A., 2003). (This paper is meant to be an introduction; for a thorough review see Meerlo et al 2008 and Steiger 2003). Briefly, sleep processes interact with the periphery via the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal axis (HPA). Several neural-endocrine substances have been identified to mediate the sleep response.

Typically the function of these substrates can be portrayed both directly and indirectly either via the HPA axis or the autonomic nervous system (Chang, F. C. & Opp, M. R., 2001).

Various hormones are among the substrates important to the sleep-wake cycle. Melatonin, a hormone produced by the pineal gland, is circadian rhythm driven by the superchiasmatic nucleus (SCN) of the hypothalamus. Although the precise role of melatonin in human physiology is poorly understood (Kunz, D., Mahlberg, R., Muller, C., Tilmann, A., & Bes, F., 2004), it nevertheless is recognized as a primary influence on the internal clock, in that it has phase shifting ability and is thought to assist with the synchronization of circadian rhythms that have been disrupted, i.e. jetlag (Kunz, D., Mahlberg, R., Muller, C., Tilmann, A., & Bes, F., 2004). It is also thought to stimulate various components of the immune system, such as enhancing humoral and cellular immune responses (Haimov, I., Shochat, T., & Lavie, P., 1997; Haimov, I. & Lavie, P., 1997; Maestroni, G. J., 1993). Specifically, melatonin has been suggested to regulate IL-4 production in bone marrow T-helper cells (Maestroni, G. J., Hertens, E., Galli, P., Conti, A., & Pedrinis, E., 1996) as well as interact with IL-2 in the modulation of host antitumor immune responses (Lissoni, P., Rovelli, F., Meregalli, S., Fumagalli, L., Musco, F., Brivio, F., Brivio, O., & Esposito, G., 1997). Lastly, evidence relating the stimulation of IL-2 secretion during the night with melatonin suggests that the IL-2 blood concentration could depend in part on the action of melatonin (Lissoni, P., Rovelli, F., Brivio, F., Brivio, O., & Fumagalli, L., 1998).

The sex steroid hormones are also involved in the sleep-wake cycle. Progesterone exhibits soporific properties (Baker, F. C., Mitchell, D., & Driver, H. S., 2001; Lancel, M., Faulhaber, J., Schiffelholz, T., Romeo, E., Di Michele, F., Holsboer, F., & Rupprecht, R., 1997; Lancel, M., Faulhaber, J., Holsboer, F., & Rupprecht, R., 1996) and acts as an immunosuppressive agent on lymphocytes (Moldofsky, H., Lue, F. A., Shahal, B., Jiang, C. G., & Gorczynski, R. M., 1995). Healthy young women have more stage 2 sleep, higher spindle frequency activity, and less rapid-eye movement (REM) sleep when progesterone predominates in the luteal phase (Driver, H. S. & Baker, F. C., 1998). This is further evidenced by comparing young women who are naturally cycling to those taking oral contraceptives (Baker, F. C., Mitchell, D., & Driver, H. S., 2001). The role of estrogen in sleep, on the other hand, is informed primarily through studies of peri- and post-menopausal women. The poor sleep quality commonly reported among these women is significantly reduced when given estrogen replacement therapies (Hachul, H. et al., 2008; Polo-Kantola, P., Erkkola, R., Helenius, H., Irjala, K., & Polo, O., 1998; Saletu-Zyhlarz, G., Anderer, P., Gruber, G., Mandl, M., Gruber, D., Metka, M., Huber, J., Oettel, M., Graser, T., Abu-Bakr, M. H., Gratzhofer, E., & Saletu, B., 2003). Like progesterone, estrogen also has immunoenhancing properties as evidenced by a reduction of IL-6 levels in postmenopausal women undergoing estrogen replacement therapy, indicating a lower cardiovascular disease risk (Papanicolaou, D. A. & Vgontzas, A. N., 2000).

The SNS and its substrates are also significantly involved in the sleep-wake cycle. Catecholamines, adrenaline (epinephrine) and noradrenaline (norepinephrine), are important for regulation of energy balance and cardiovascular function (Meerlo, P., Sgoifo, A., & Suchecki, D., 2008). Sleep deprivation and fragmentation are associated with an increase in autonomic sympathetic activation and increased catecholamine levels (Irwin, M., Clark, C., Kennedy, B., Christian, G. J., & Ziegler, M., 2003; Meerlo, P., Sgoifo, A., & Suchecki, D., 2008). This is especially evidenced by increased autonomic activation among individuals with restless legs syndrome (Guggisberg, A. G., Hess, C. W., & Mathis, J., 2007) and insomnia (Irwin, M., Clark, C., Kennedy, B., Christian, G. J., & Ziegler, M., 2003). Since increased catecholamine levels are associated with unfavorable changes in the autonomic system, understanding the consequences of disturbed sleep as it relates to metabolism and cardiac health is important.

A vast amount of research has been conducted on the relationships between sleep and components of the HPA axis (e.g. CRH, ACTH and cortisol) (Born, J. et al., 1986; Born, J., Spath-Schwalbe, E., Schwakenhofer, H., Kern, W., & Fehm, H. L., 1989; Chang, F. C. & Opp, M. R., 2001; Meerlo, P., Sgoifo, A., & Suchecki, D., 2008; Schmid, D. A. et al., 2006; Vgontzas, A. N. & Chrousos, G. P., 2002). It is clear, for instance, that a bi-directional relationship exists between sleep and cortisol. Sleep deprivation/restriction alters cortisol production (Salin-Pascual, R. J., Ortega-Soto, H., Huerto-Delgadillo, L., Camacho-Arroyo, I., Roldan-Roldan, G., & Tamarkin, L., 1988). Likewise, cortisol administration increases NREM sleep and decreases REM sleep (Schmid, D. A., Wichniak, A., Uhr, M., Ising, M., Brunner, H., Held, K., Weikel, J. C., Sonntag, A., & Steiger, A., 2006). The relationship between sleep, the HPA axis, and stress is simplified by the concept that sleep is important for the recovery from stress. During stressful periods, the HPA axis secretes an excess of pituitary-adrenal hormones that mediate susceptibility to disease. If pituitary-adrenal activity is diminished during sleep, the potential for recovery is increased because, from a psychoneuroendocrinological perspective, early sleep can be regarded as the only period during the day that is free of stress (Born, J., Kern, W., Bieker, K., Fehm-Wolfsdorf, G., Schiebe, M., & Fehm, H. L., 1986; Born, J., Spath-Schwalbe, E., Schwakenhofer, H., Kern, W., & Fehm, H. L., 1989). However, HPA activity is only halted during the first few hours of sleep, (e.g. during SWS) (Born, J. et al., 1986; Born, J., Muth, S., & Fehm, H. L., 1988). Viewing sleep as a stress-free period implores one to acknowledge that sleep disruption may be a stressor. For acute stressors, the immune response, via the HPA axis, may be enhanced. In a sleep paradigm, this is delineated by the observance of increased monocytes and cytokine levels in the blood of individuals who were sleep deprived for one night (Born, J., Lange, T., Hansen, K., Molle, M., & Fehm, H. L., 1997). However, chronic sleep disruption exhibits disinhibited HPA activity and subsequent dysregulation and reduced cytokine production (Born, J., 1999; Born, J. & Fehm, H. L., 2000).

While each component of the HPA axis is important, the majority of clinical evidence stems from investigations of sleep and cortisol. It is commonly assessed because it is the final product of the HPA axis and is easy to measure. Data consistently show that poor sleep may increase cortisol output leading to higher daily levels (Leproult, R., Copinschi, G., Buxton, O., & Van, Cauter E., 1997; Okun, M. L., Krafty, R. T., Buysse, D. J., Monk, T. H., Reynolds, C. F., III, Begley, A., & Hall, M., 2009; Redwine, L., Hauger, R. L., Gillin, J. C., & Irwin, M., 2000; Spiegel, K., Leproult, R., & Van Cauter, E., 1999; Vgontzas, A. N. et al., 2003) or lead to alterations in the cortisol awakening response (CAR) (the rise from waking levels to 30-45 minutes post-wake) (Backhaus, J., Junghanns, K., & Hohagen, F., 2004; Dockray, S., Bhattacharyya, M. R., Molloy, G. J., & Steptoe, A., 2008; Federenko, I. et al., 2004; Griefahn, B. & Robens, S., 2008; Okun, M. L. et al., 2009; Van, Cauter E., Leproult, R., & Kupfer, D. J., 1996; Williams, E., Magid, K., & Steptoe, A., 2005). However, the diurnal rhythm of cortisol output is primarily regulated by circadian processes and is minimally modulated by sleep (Leproult, R., Copinschi, G., Buxton, O., & Van, Cauter E., 1997). These alterations may have consequences for the body's stress response to effectively respond to the daily demands, and ultimately for an effective immune response.

Summary

Sleep is a necessary and ubiquitous behavior. Like eating and drinking, without it we will eventually die. Sleep is affected by various psychosocial factors, stress and daily routines; and it similarly affects all areas of life. Stress, socioeconomic status, race and age, for example, are known contributors to poor sleep. Poor sleep can also increase subjective stress levels and "biologically age" people. Mounting evidence support the hypothesis that chronically restricted and disrupted sleep have significant health consequences. By dysregulating immune and endocrine pathways, sleep may contribute to increased risk of

inflammatory mediated diseases, including cardiovascular disease, diabetes, metabolic syndrome and depression. Although still in its early stages, research supports a role for adequate and sufficient sleep in order to promote effective immune functioning. Since sleep is a modifiable behavior and responds positively to interventions, there is great potential for reduction of disease risk via improved sleep and positive alterations in immune and endocrine pathways. These studies are hopefully slated to be conducted.

Future Directions

Myriad correlates of health have been identified, including gender, age, ethnicity, socioeconomic status, depression and nutrition. Some correlates are constant and unchangeable, while others can be modified. Sleep as a correlate of health is unique in that it is a constant (we must sleep) but it is modifiable (we can voluntarily alter our sleep). Thus, the evaluation of sleep provides a unique opportunity to not only understand group differences (e.g. good sleepers vs poor sleepers), but how the behavior of sleep contributes to health. Moreover, there is growing evidence that manipulation of sleep behaviors/patterns can influence biological variables well-established to impact health (Bryant, P. A., Trinder, J., & Curtis, N., 2004; Cakirbay, H., Bilici, M., Kavakci, O., Cebi, A., Guler, M., & Tan, U., 2004; Cruess, D. G., Antoni, M. H., Gonzalez, J., Fletcher, M. A., Klimas, N., Duran, R., Ironson, G., & Schneiderman, N., 2003; Faraut, B. et al., 2011; Hall, M., Baum, A., Buysse, D. J., Prigerson, H. G., Kupfer, D. J., & Reynolds, C. F., 1998; Landis, C. A., Lentz, M. J., Tsuji, J., Buchwald, D., & Shaver, J. L., 2004; Savard, J., Simard, S., Ivers, H., & Morin, C. M., 2005; Wright, C. E., Erblich, J., Valdimarsdottir, H. B., & Bovbjerg, D. H., 2006). In order to truly understand the implications of disturbed sleep on health both the immediate and long-term effects of disturbed sleep on immunocompetence need to be ascertained through longitudinal study designs. The combination of a prospective design with elements of an epidemiologic study is warranted. Finally, promising data indicate that sleep can be successfully modified with long-lasting positive changes (Chen, H. Y., Chiang, C. K., Wang, H. H., Hung, K. Y., Lee, Y. J., Peng, Y. S., Wu, K. D., & Tsai, T. J., 2008; Davidson, J. R., 2009; Driscoll, H. C., Serody, L., Patrick, S., Maurer, J., Bensasi, S., Houck, P. R., Mazumdar, S., Nofzinger, E. A., Bell, B., Nebes, R. D., Miller, M. D., & Reynolds, C. F., III, 2008; Edinger, J. D., Olsen, M. K., Stechuchak, K. M., Means, M. K., Lineberger, M. D., Kirby, A., & Carney, C. E., 2009; Epstein, D. R. & Dirksen, S. R., 2007; Germain, A., Moul, D. E., Franzen, P. L., Miewald, J. M., Reynolds, C. F., III, Monk, T. H., & Buysse, D. J., 2006; Lichstein, K. L., 2006). The biological consequences of behavioral interventions must be comprehensively evaluated. It will be these future studies that provide new information as to how sleep contributes to health, and which aspects of sleep provide the most promising occasions to intervene.

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Reference List

- Adam K. Sleep as a restorative process and a theory to explain why. *Progress in Brain Research*. 1980; 53:289–305. [PubMed: 7005947]
- Akerstedt T, Nilsson PM. Sleep as restitution: an introduction. *Journal of Internal Medicine*. 2003; 254:6–12. [PubMed: 12823638]
- Alvarez GG, Ayas NT. The impact of daily sleep duration on health: a review of the literature. *Progress in Cardiovascular Nursing*. 2004; 19:56–59. [PubMed: 15133379]
- Ancoli-Israel S. The impact and prevalence of chronic insomnia and other sleep disturbances associated with chronic illness. *American Journal ManagedCare*. 2006; 12:S221–S229.

- Andersen ML, Martins PJ, D'Almeida V, Bignotto M, Tufik S. Endocrinological and catecholaminergic alterations during sleep deprivation and recovery in male rats. *Journal of Sleep Research*. 2005; 14:83–90. [PubMed: 15743338]
- Backhaus J, Junghanns K, Hohagen F. Sleep disturbances are correlated with decreased morning awakening salivary cortisol. *Psychoneuroendocrinology*. 2004; 29:1184–1191. [PubMed: 15219642]
- Baker FC, Mitchell D, Driver HS. Oral contraceptives alter sleep and raise body temperature in young women. *Pflügers Archives*. 2001; 442:729–737. [PubMed: 11512029]
- Ballieux RE. The mind and the immune system. *Theoretical Medicine*. 1994; 15:387–395. [PubMed: 7886633]
- Bautista LE. Inflammation, endothelial dysfunction, and the risk of high blood pressure: epidemiologic and biological evidence. *Journal Human Hypertension*. 2003; 17:223–230.
- Benca R, Quintas J. Sleep and host defenses: A review. *Sleep*. 1997; 20:1027–1037. [PubMed: 9456469]
- Benderly M, Haim M, Boyko V, Tanne D, Behar S, Matas Z, Zimlichman R, Goldbourt U. C-Reactive Protein Distribution and Correlates among Men and Women with Chronic Coronary Heart Disease. *Cardiology*. 2007; 107:345–353. [PubMed: 17283424]
- Born, J. Sleep and immune functions. In: Schedlowski, M.; Tewes, U., editors. *Psychoneuroimmunology: An interdisciplinary introduction*. Kluwer Academic/Plenum Publishers; New York: 1999. p. 417–442.
- Born J, Fehm HL. The neuroendocrine recovery function of sleep. *Noise and Health*. 2000; 2:25–38. [PubMed: 12689469]
- Born J, Kern W, Bieber K, Fehm-Wolfsdorf G, Schiebe M, Fehm HL. Night-time plasma cortisol secretion is associated with specific sleep stages. *Biological Psychiatry*. 1986; 21:1415–1424. [PubMed: 3790626]
- Born J, Lange T, Hansen K, Molle M, Fehm HL. Effects of sleep and circadian rhythm on human circulating immune cells. *Journal of Immunology*. 1997; 158:4454–4464.
- Born J, Muth S, Fehm HL. The significance of sleep onset and slow wave sleep for nocturnal release of growth hormone and cortisol. *Psychoneuroendocrinology*. 1988; 13:233–243. [PubMed: 3406323]
- Born J, Spath-Schwalbe E, Schwakenhofer H, Kern W, Fehm HL. Influences of corticotropin-releasing hormone, adrenocorticotropin, and cortisol on sleep in normal man. *Journal of Clinical Endocrinology and Metabolism*. 1989; 68:904–911. [PubMed: 2541159]
- Bryant PA, Trinder J, Curtis N. Sick and tired: Does sleep have a vital role in the immune system? *Nature Reviews Immunology*. 2004; 4:457–467.
- Buysse DJ, Cheng Y, Germain A, Moul DE, Franzen PL, Fletcher M, Monk TH. Night-to-night sleep variability in older adults with and without chronic insomnia. *Sleep Medicine*. 2010; 11:56–64. [PubMed: 19962939]
- Cakirbay H, Bilici M, Kavakci O, Cebi A, Guler M, Tan U. Sleep quality and immune functions in rheumatoid arthritis patients with and without major depression. *International Journal of Neuroscience*. 2004; 114:245–256. [PubMed: 14702212]
- Carrier J, Land S, Buysse DJ, Kupfer DJ, Monk TH. The effects of age and gender on sleep EEG power spectral density in the middle years of life (ages 20–60 years old). *Psychophysiology*. 2001; 38:232–242. [PubMed: 11347869]
- Carskadon, M.; Dement, WC. Normal Human Sleep: An Overview. In: Kryger, MH.; Roth, T.; Dement, WC., editors. *Principles and Practice of Sleep Medicine*. fourth ed. Elsevier Saunders; Philadelphia: 2005. p. 13–23.
- Cesari M, Penninx BW, Newman AB, Kritchevsky SB, Nicklas BJ, Sutton-Tyrrell K, Tracy RP, Rubin SM, Harris TB, Pahor M. Inflammatory markers and cardiovascular disease (The Health, Aging and Body Composition [Health ABC] Study). *American Journal of Cardiology*. 2003; 92:522–528. [PubMed: 12943870]
- Chang FC, Opp MR. Corticotropin-releasing hormone (CRH) as a regulator of waking. *Neuroscience and Biobehavioral Reviews*. 2001; 25:445–453. [PubMed: 11566481]

- Chen HY, Chiang CK, Wang HH, Hung KY, Lee YJ, Peng YS, Wu KD, Tsai TJ. Cognitive-behavioral therapy for sleep disturbance in patients undergoing peritoneal dialysis: a pilot randomized controlled trial. *American Journal Kidney Disease*. 2008; 52:314–323.
- Cohen S, Doyle WJ, Alper CM, Janicki-Deverts D, Turner RB. Sleep habits and susceptibility to the common cold. *Archives of Internal Medicine*. 2009; 169:62–67. [PubMed: 19139325]
- Cruess DG, Antoni MH, Gonzalez J, Fletcher MA, Klimas N, Duran R, Ironson G, Schneiderman N. Sleep disturbance mediates the association between psychological distress and immune status among HIV-positive men and women on combination antiretroviral therapy. *Journal of Psychosomatic Research*. 2003; 54:185–189. [PubMed: 12614827]
- Davidson JR. Insomnia treatment options for women. *Obstetrics & Gynecology Clinics of North America*. 2009; 36:831–841. [PubMed: 19944303]
- Diamanti-Kandarakis E, Alexandraki K, Piperi C, Protogerou A, Katsikis I, Paterakis T, Lekakis J, Panidis D. Inflammatory and endothelial markers in women with polycystic ovary syndrome. *European Journal Clinical Investigation*. 2006; 36:691–697.
- Dimitrov S, Lange T, Tieken S, Fehm HL, Born J. Sleep associated regulation of T helper 1/T helper 2 cytokine balance in humans. *Brain, Behavior, and Immunity*. 2004; 18:341–348.
- Dinges DF, Douglas SD, Zaugg L, Campbell DE, McMann JM, Whitehouse WG, Orne EC, Kapoor SC, Icaza E, Orne MT. Leukocytosis and natural killer cell function parallel neurobehavioral fatigue induced by 64 hours of sleep deprivation. *Journal of Clinical Investigation*. 1994; 93:1930–1939. [PubMed: 7910171]
- Dockray S, Bhattacharyya MR, Molloy GJ, Steptoe A. The cortisol awakening response in relation to objective and subjective measures of waking in the morning. *Psychoneuroendocrinology*. 2008; 33:77–82. [PubMed: 17996380]
- Driscoll HC, Serody L, Patrick S, Maurer J, Bensasi S, Houck PR, Mazumdar S, Nofzinger EA, Bell B, Nebes RD, Miller MD, Reynolds CF III. Sleeping well, aging well: a descriptive and cross-sectional study of sleep in “successful agers” 75 and older. *American Journal of Geriatric Psychiatry*. 2008; 16:74–82. [PubMed: 18070833]
- Driver HS, Baker FC. Menstrual factors in sleep. *Sleep Medicine Reviews*. 1998; 2:213–229. [PubMed: 15310493]
- Edinger JD, Olsen MK, Stechuchak KM, Means MK, Lineberger MD, Kirby A, Carney CE. Cognitive behavioral therapy for patients with primary insomnia or insomnia associated predominantly with mixed psychiatric disorders: a randomized clinical trial. *Sleep*. 2009; 32:499–510. [PubMed: 19413144]
- Epstein DR, Dirksen SR. Randomized trial of a cognitive-behavioral intervention for insomnia in breast cancer survivors. *Oncology Nursing Forum*. 2007; 34:E51–E59. [PubMed: 17878117]
- Everson CA. Clinical assessment of blood leukocytes, serum cytokines, and serum immunoglobulins as responses to sleep deprivation in laboratory rats. *American Journal of Physiology Regulatory Integrative Comparative Physiology*. 2005; 289:R1054–R1063.
- Faraut B, Boudjeltia KZ, Dyzma M, Rousseau A, David E, Stenuit P, Franck T, Van AP, Vanhaeverbeek M, Kerkhofs M. Benefits of napping and an extended duration of recovery sleep on alertness and immune cells after acute sleep restriction. *Brain, Behavior, and Immunity*. 2011; 25:16–24.
- Federenko I, Wust S, Hellhammer DH, Dechoux R, Kumsta R, Kirschbaum C. Free cortisol awakening responses are influenced by awakening time. *Psychoneuroendocrinology*. 2004; 29:174–184. [PubMed: 14604599]
- Frey DJ, Fleshner M, Wright KP Jr. The effects of 40 hours of total sleep deprivation on inflammatory markers in healthy young adults. *Brain, Behavior, and Immunity*. 2007; 21:1050–1057.
- Fuller PM, Gooley JJ, Saper CB. Neurobiology of the sleep-wake cycle: sleep architecture, circadian regulation, and regulatory feedback. *Journal of Biological Rhythms*. 2006; 21:482–493. [PubMed: 17107938]
- Gangwisch JE, Heymsfield SB, Boden-Albala B, Buijs RM, Kreier F, Pickering TG, Rundle AG, Zammit GK, Malaspina D. Short sleep duration as a risk factor for hypertension: analyses of the first National Health and Nutrition Examination Survey. *Hypertension*. 2006; 47:833–839. [PubMed: 16585410]

- Garcia RG, Celedon J, Sierra-Laguado J, Alarcon MA, Luengas C, Silva F, Arenas-Mantilla M, Lopez-Jaramillo P. Raised C-reactive protein and impaired flow-mediated vasodilation precede the development of preeclampsia. *American Journal Hypertension*. 2007; 20:98–103.
- Germain A, Moul DE, Franzen PL, Miewald JM, Reynolds CF III, Monk TH, Buysse DJ. Effects of a brief behavioral treatment for late-life insomnia: preliminary findings. *Journal of Clinical Sleep Medicine*. 2006; 2:403–406. [PubMed: 17557467]
- Griefahn B, Robens S. The cortisol awakening response: a pilot study on the effects of shift work, morningness and sleep duration. *Psychoneuroendocrinology*. 2008; 33:981–988. [PubMed: 18650024]
- Guggisberg AG, Hess CW, Mathis J. The significance of the sympathetic nervous system in the pathophysiology of periodic leg movements in sleep. *Sleep*. 2007; 30:755–766. [PubMed: 17580597]
- Haack M, Sanchez E, Mullington JM. Elevated inflammatory markers in response to prolonged sleep restriction are associated with increased pain experience in healthy volunteers. *Sleep*. 2007; 30:1145–1152. [PubMed: 17910386]
- Hachul H, Bittencourt LR, Andersen ML, Haidar MA, Baracat EC, Tufik S. Effects of hormone therapy with estrogen and/or progesterone on sleep pattern in postmenopausal women. *International Journal Gynaecology Obstetrics*. 2008; 103:207–212.
- Haimov I, Lavie P. Melatonin - a chronobiotic and soporific hormone. *Arcives Gerontology and Geriatrics*. 1997; 24:167–173.
- Haimov I, Shochat T, Lavie P. Melatonin--a possible link between sleep and the immune system. *Israel Journal Medical Sciences*. 1997; 33:246–250.
- Hall, M. Behavioral medicine and sleep: Concepts, measures and methods. In: Steptoe, A., editor. *Handbook of Behavioral Medicine: Methods and Applications*. Springer; 2010.
- Hall, M.; Okun, ML.; Atwood, CW.; Buysse, DJ.; Strollo, PJ. Measurement of sleep by polysomnography. In: Luecken, LL.; Gallo, LC., editors. *Handbook of Physiological Research Methods in Health Psychology*. Sage Publications; 2008. p. 341–367.
- Hall M, Baum A, Buysse DJ, Prigerson HG, Kupfer DJ, Reynolds CF. Sleep as a mediator of the stress-immune relationship. *Psychosomatic Medicine*. 1998; 60:48–51. [PubMed: 9492239]
- Hall MH, Matthews KA, Kravitz HM, Gold EB, Buysse DJ, Bromberger JT, Owens JF, Sowers M. Race and financial strain are independent correlates of sleep in midlife women: the SWAN sleep study. *Sleep*. 2009; 32:73–82. [PubMed: 19189781]
- Hogan D, Morrow JD, Smith EM, Opp MR. Interleukin-6 alters sleep of rats. *Journal of Neuroimmunology*. 2003; 137:59–66.
- Irwin M. Effects of sleep and sleep loss on immunity and cytokines. *Brain, Behavior, and Immunity*. 2002; 16:503–512.
- Irwin M, Clark C, Kennedy B, Christian GJ, Ziegler M. Nocturnal catecholamines and immune function in insomniacs, depressed patients, and control subjects. *Brain, Behavior, and Immunity*. 2003; 17:365–372.
- Irwin MR, Wang M, Campomayor CO, Collado-Hidalgo A, Cole S. Sleep deprivation and activation of morning levels of cellular and genomic markers of inflammation. *Archives of Internal Medicine*. 2006; 166:1756–1762. [PubMed: 16983055]
- Kapsimalis F, Basta M, Varouchakis G, Gourgoulialis K, Vgontzas A, Kryger M. Cytokines and pathological sleep. *Sleep Medicine*. 2007; 9:603–614. [PubMed: 18024171]
- Kilroy GE, Foster SJ, Wu X, Ruiz J, Sherwood S, Heifetz A, Ludlow JW, Stricker DM, Potiny S, Green P, Halvorsen YD, Cheatham B, Storms RW, Gimble JM. Cytokine profile of human adipose-derived stem cells: expression of angiogenic, hematopoietic, and pro-inflammatory factors. *Journal of Cell Physiology*. 2007; 122:702–709.
- Knutson KL, Rathouz PJ, Yan LL, Liu K, Lauderdale DS. Intra-individual daily and yearly variability in actigraphically recorded sleep measures: the CARDIA study. *Sleep*. 2007; 30:793–796. [PubMed: 17580601]
- Koenig W. Update on C-reactive protein as a risk marker in cardiovascular disease. *Kidney International Supplement*. 2003:S58–S61. [PubMed: 12694310]

- Kunz D, Mahlberg R, Muller C, Tilmann A, Bes F. Melatonin in patients with reduced REM sleep duration: two randomized controlled trials. *Journal Clinical and Endocrinological Metabolism*. 2004; 89:128–134.
- Lancel M, Faulhaber J, Holsboer F, Rupprecht R. Progesterone induces changes in sleep comparable to those of agonistic GABAA receptor modulators. *American Journal of Physiology*. 1996; 271:E763–E772. [PubMed: 8897866]
- Lancel M, Faulhaber J, Schiffelholz T, Romeo E, Di Michele F, Holsboer F, Rupprecht R. Allopregnanolone affects sleep in a benzodiazepine-like fashion. *Journal of Pharmacology and Experimental Therapeutics*. 1997; 282:1213–1218. [PubMed: 9316828]
- Landis CA, Lentz MJ, Tsuji J, Buchwald D, Shaver JL. Pain, psychological variables, sleep quality, and natural killer cell activity in midlife women with and without fibromyalgia. *Brain, Behavior, and Immunity*. 2004; 18:304–313.
- Lange T, Dimitrov S, Born J. Effects of sleep and circadian rhythm on the human immune system. *Annals of the New York Academy of Sciences*. 2010; 1193:48–59. [PubMed: 20398008]
- Lange T, Perras B, Fehm HL, Born J. Sleep enhances the human antibody response to hepatitis A vaccination. *Psychosomatic Medicine*. 2003; 65:831–835. [PubMed: 14508028]
- Lappas M, Permezel M, Rice GE. Release of proinflammatory cytokines and 8-isoprostane from placenta, adipose tissue, and skeletal muscle from normal pregnant women and women with gestational diabetes mellitus. *Journal Clinical and Endocrinology and Metabolism*. 2004; 89:5627–5633.
- Leproult R, Copinschi G, Buxton O, Van CE. Sleep loss results in an elevation of cortisol levels the next evening. *Sleep*. 1997; 20:865–870. [PubMed: 9415946]
- Lichstein KL. Behavioral intervention for special insomnia populations: Hypnotic-dependent insomnia and comorbid insomnia. *Sleep Medicine*. 2006; 7(Suppl 1):S27–S31.
- Lim J, Dinges DF. Sleep deprivation and vigilant attention. *Annals of the New York Academy of Sciences*. 2008; 1129:305–322. [PubMed: 18591490]
- Lissoni P, Rovelli F, Brivio F, Brivio O, Fumagalli L. Circadian secretions of IL-2, IL-12, IL-6 and IL-10 in relation to the light/dark rhythm of the pineal hormone melatonin in healthy humans. *Natural Immunity*. 1998; 16:1–5. [PubMed: 9789119]
- Lissoni P, Rovelli F, Meregalli S, Fumagalli L, Musco F, Brivio F, Brivio O, Esposti G. Melatonin as a new possible anti-inflammatory agent. *Journal of Biological Regulators and Homeostatic Agents*. 1997; 11:157–159. [PubMed: 9582617]
- Liukkonen T, Rasanen P, Ruokonen A, Laitinen J, Jokelainen J, Leinonen M, Meyer-Rochow VB, Timonen M. C-reactive protein levels and sleep disturbances: observations based on the Northern Finland 1966 Birth Cohort study. *Psychosomatic Medicine*. 2007; 69:756–761. [PubMed: 17942834]
- Maestroni GJ. The immunoneuroendocrine role of melatonin. *Journal of Pineal Research*. 1993; 14:1–10. [PubMed: 8483103]
- Maestroni GJ, Hertens E, Galli P, Conti A, Pedrinis E. Melatonin-induced T-helper cell hematopoietic cytokines resembling both interleukin-4 and dynorphin. *Journal of Pineal Research*. 1996; 21:131–139. [PubMed: 8981257]
- Majde JA, Krueger JM. Links between the innate immune system and sleep. *Journal of Allergy and Clinical Immunology*. 2005; 116:1188–1198. [PubMed: 16337444]
- McDade TW, Hawkey LC, Cacioppo JT. Psychosocial and behavioral predictors of inflammation in middle-aged and older adults: the Chicago health, aging, and social relations study. *Psychosomatic Medicine*. 2006; 68:376–381. [PubMed: 16738067]
- McEwen BS. Sleep deprivation as a neurobiologic and physiologic stressor: Allostasis and allostatic load. *Metabolism: Clinical and Experimental*. 2006; 55:S20–S23. [PubMed: 16979422]
- Meerlo P, Sgoifo A, Suchecki D. Restricted and disrupted sleep: Effects on autonomic function, neuroendocrine stress systems and stress responsivity. *Sleep Medicine Reviews*. 2008; 12:197–210. [PubMed: 18222099]
- Meier-Ewert HK, Ridker PM, Rifai N, Price N, Dinges DF, Mullington JM. Absence of diurnal variation of C-reactive protein concentrations in healthy human subjects. *Clinical Chemistry*. 2001; 47:426–430. [PubMed: 11238292]

- Meier-Ewert HK, Ridker PM, Rifai N, Regan MM, Price NJ, Dinges DF, Mullington JM. Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk. *Journal of the American College of Cardiology*. 2004; 43:678–683. [PubMed: 14975482]
- Meisinger C, Heier M, Lowel H, Schneider A, Doring A. Sleep duration and sleep complaints and risk of myocardial infarction in middle-aged men and women from the general population: the MONICA/KORA Augsburg cohort study. *Sleep*. 2007; 30:1121–1127. [PubMed: 17910384]
- Mezick EJ, Matthews KA, Hall M, Kamarck TW, Buysse DJ, Owens JF, Reis SE. Intra-individual variability in sleep duration and fragmentation: Associations with stress. *Psychoneuroendocrinology*. 2009; 34:1346–1354. [PubMed: 19450933]
- Miller MA, Kandala NB, Kivimaki M, Kumari M, Brunner EJ, Lowe GD, Marmot MG, Cappuccio FP. Gender differences in the cross-sectional relationships between sleep duration and markers of inflammation: Whitehall II study. *Sleep*. 2009; 32:857–864. [PubMed: 19639748]
- Moldofsky H, Lue FA, Shahal B, Jiang CG, Gorczynski RM. Diurnal sleep/wake-related immune functions during the menstrual cycle of healthy young women. *Journal of Sleep Research*. 1995; 4:150–159. [PubMed: 10607154]
- Ohayon MM, Carskadon MA, Guilleminault C, Vitiello MV. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. *Sleep*. 2004; 27:1255–1273. [PubMed: 15586779]
- Okun ML, Coussons-Read M, Hall M. Disturbed sleep is associated with increased C-reactive protein in young women. *Brain, Behavior, and Immunity*. 2009; 23:351–354.
- Okun ML, Coussons-Read ME. Sleep disruption during pregnancy: how does it influence serum cytokines? *Journal of Reproductive Immunology*. 2007; 73:158–165. [PubMed: 17074396]
- Okun ML, Hall M, Coussons-Read ME. Sleep disturbances increase interleukin-6 production during pregnancy: implications for pregnancy complications. *Reproductive Sciences*. 2007; 14:560–567. [PubMed: 17959884]
- Okun ML, Hanusa BH, Hall M, Wisner KL. Sleep complaints in late pregnancy and the recurrence of postpartum depression. *Behavioral Sleep Medicine*. 2009; 7:106–117. [PubMed: 19330583]
- Okun ML, Krafty RT, Buysse DJ, Monk TH, Reynolds CF III, Begley A, Hall M. What constitutes too long of a delay? Determining the cortisol awakening response (CAR) using self-report and PSG-assessed wake time. *Psychoneuroendocrinology*. 2009; 34:460–468. [PubMed: 19762158]
- Okun ML, Reynolds CF III, Buysse DJ, Monk TH, Mazumdar S, Begley A, Hall M. Sleep Variability, Health-Related Practices, and Inflammatory Markers in a Community Dwelling Sample of Older Adults. *Psychosomatic Medicine*. (In press).
- Olivadoti MD, Opp MR. Effects of i.c.v. administration of interleukin-1 on sleep and body temperature of interleukin-6-deficient mice. *Neuroscience*. 2008; 153:338–348. [PubMed: 18367337]
- Opp, M.; Born, J.; Irwin, M. Sleep and the Immune System. In: Ader, R., editor. *Psychoneuroimmunology*. 4th ed. Academic Press, Inc; New York: 2006. p. 539–578.
- Opp MR. Sleep and psychoneuroimmunology. *Neurologic Clinics*. 2006; 24:493–506. [PubMed: 16877120]
- Opp MR. Sleep and psychoneuroimmunology. *Immunology and Allergy Clinics of North America*. 2009; 29:295–307. [PubMed: 19389583]
- Papanicolaou DA, Vgontzas AN. Interleukin-6: the endocrine cytokine. *Journal of Clinical Endocrinology and Metabolism*. 2000; 85:1331–1333. [PubMed: 10720086]
- Patel SR, Zhu X, Storfer-Isser A, Mehra R, Jenny NS, Tracy R, Redline S. Sleep duration and biomarkers of inflammation. *Sleep*. 2009; 32:200–204. [PubMed: 19238807]
- Pollmacher T, Schuld A, Kraus T, Haack M, Hinze-Selch D, Mullington J. Experimental immunomodulation, sleep, and sleepiness in humans. *Annals of the New York Academy of Sciences*. 2000; 917:488–499. [PubMed: 11268376]
- Polo-Kantola P, Erkkola R, Helenius H, Irjala K, Polo O. When does estrogen replacement therapy improve sleep quality? *American Journal of Obstetrics and Gynecology*. 1998; 178:1002–1009. [PubMed: 9609575]

- Redwine L, Hauger RL, Gillin JC, Irwin M. Effects of sleep and sleep deprivation on interleukin-6, growth hormone, cortisol, and melatonin levels in humans. *Journal of Clinical Endocrinology and Metabolism*. 2000; 85:3597–3603. [PubMed: 11061508]
- Roehrs, T.; Carskadon, MA.; Dement, WC.; Roth, T. Daytime Sleepiness and Alertness. In: Kryger, MH.; Roth, T.; Dement, WC., editors. *Principles and Practice of Sleep Medicine*. fourth edition ed. Elsevier Saunders; Philadelphia: 2005. p. 39-50.
- Ruiz FS, Andersen ML, Martins RC, Zager A, Lopes JD, Tufik S. Immune alterations after selective rapid eye movement or total sleep deprivation in healthy male volunteers. *Innate Immunity*. (In press).
- Sakami S, Ishikawa T, Kawakami N, Haratani T, Fukui A, Kobayashi F, Fujita O, Araki S, Kawamura N. Coemergence of insomnia and a shift in the Th1/Th2 balance toward Th2 dominance. *Neuroimmunomodulation*. 2002; 10:337–343. [PubMed: 12907840]
- Saletu-Zyhlarz G, Anderer P, Gruber G, Mandl M, Gruber D, Metka M, Huber J, Oettel M, Graser T, Abu-Bakr MH, Gratzhofer E, Saletu B. Insomnia related to postmenopausal syndrome and hormone replacement therapy: sleep laboratory studies on baseline differences between patients and controls and double-blind, placebo-controlled investigations on the effects of a novel estrogen-progestogen combination (Climodien, Lafamme) versus estrogen alone. *Journal of Sleep Research*. 2003; 12:239–254. [PubMed: 12941063]
- Salin-Pascual RJ, Ortega-Soto H, Huerto-Delgadillo L, Camacho-Arroyo I, Roldan-Roldan G, Tamarkin L. The effect of total sleep deprivation on plasma melatonin and cortisol in healthy human volunteers. *Sleep*. 1988; 11:362–369. [PubMed: 3206055]
- Sari I, Davutoglu V, Ozbala B, Ozer O, Baltaci Y, Yavuz S, Aksoy M. Acute sleep deprivation is associated with increased electrocardiographic P-wave dispersion in healthy young men and women. *Pacing and Clinical Electrophysiology*. 2008; 31:438–442. [PubMed: 18373762]
- Savard J, Laroche L, Simard S, Ivers H, Morin CM. Chronic insomnia and immune functioning. *Psychosomatic Medicine*. 2003; 65:211–221. [PubMed: 12651988]
- Savard J, Simard S, Ivers H, Morin CM. Randomized study on the efficacy of cognitive-behavioral therapy for insomnia secondary to breast cancer, part II: Immunologic effects. *Journal of Clinical Oncology*. 2005; 23:6097–6106. [PubMed: 16135476]
- Schmid DA, Wichniak A, Uhr M, Ising M, Brunner H, Held K, Weikel JC, Sonntag A, Steiger A. Changes of sleep architecture, spectral composition of sleep EEG, the nocturnal secretion of cortisol, ACTH, GH, prolactin, melatonin, ghrelin, and leptin, and the DEX-CRH test in depressed patients during treatment with mirtazapine. *Neuropsychopharmacology*. 2006; 31:832–844. [PubMed: 16237393]
- Spiegel K, Knutson K, Leproult R, Tasali E, Van Cauter E. Sleep loss: a novel risk factor for insulin resistance and Type 2 diabetes. *Journal of Applied Physiology*. 2005; 99:2008–2019. [PubMed: 16227462]
- Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet*. 1999; 354:1435–1439. [PubMed: 10543671]
- Spiegel K, Sheridan JF, Van Cauter E. Effect of sleep deprivation on response to immunization. *Journal of the American Medical Association*. 2002; 287:1471–1472. [PubMed: 12243633]
- Spiegel K, Tasali E, Penev P, Van Cauter E. Brief communication: Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Annals of Internal Medicine*. 2004; 141:846–850. [PubMed: 15583226]
- Steiger A. Sleep and endocrinology. *Journal of Internal Medicine*. 2003; 254:13–22. [PubMed: 12823639]
- Stricker JL, Brown GG, Wetherell LA, Drummond SP. The impact of sleep deprivation and task difficulty on networks of fMRI brain response. *International Neuropsychological Society*. 2006; 12:591–597.
- van Mark A, Weiler SW, Schroder M, Otto A, Jauch-Chara K, Groneberg DA, Spallek M, Kessel R, Kalsdorf B. The impact of shift work induced chronic circadian disruption on IL-6 and TNF-alpha immune responses. *Journal of Occupational Medicine and Toxicology*. 2010; 5:18. [PubMed: 20602750]

- Van CE, Leproult R, Kupfer DJ. Effects of gender and age on the levels and circadian rhythmicity of plasma cortisol. *Journal of Clinical Endocrinology and Metabolism*. 1996; 81:2468–2473. [PubMed: 8675562]
- Vgontzas AN, Chrousos GP. Sleep, the hypothalamic-pituitary-adrenal axis, and cytokines: multiple interactions and disturbances in sleep disorders. *Endocrinology and Metabolism Clinics of North America*. 2002; 31:15–36. [PubMed: 12055986]
- Vgontzas AN, Pejovic S, Zoumakis E, Lin HM, Bixler EO, Basta M, Fang J, Sarrigiannidis A, Chrousos GP. Daytime napping after a night of sleep loss decreases sleepiness, improves performance, and causes beneficial changes in cortisol and interleukin-6 secretion. *American Journal of Physiology Endocrinology and Metabolism*. 2007; 292:E253–E261. [PubMed: 16940468]
- Vgontzas AN, Zoumakis E, Bixler EO, Lin HM, Follett H, Kales A, Chrousos GP. Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. *Journal of Clinical Endocrinology and Metabolism*. 2004; 89:2119–2126. [PubMed: 15126529]
- Vgontzas AN, Zoumakis M, Bixler EO, Lin HM, Prolo P, Vela-Bueno A, Kales A, Chrousos GP. Impaired nighttime sleep in healthy old versus young adults is associated with elevated plasma interleukin-6 and cortisol levels: physiologic and therapeutic implications. *J Clinical Endocrinology and Metabolism*. 2003; 88:2087–2095.
- Vgontzas AN, Zoumakis M, Papanicolaou DA, Prolo P, Vela-Bueno A, Kales A, Chrousos GP. Chronic insomnia is associated with a shift in interleukin-6 and tumor necrosis factor secretion from nighttime to daytime. *Metabolism: Clinical and Experimental*. 2002; 51:887–892. [PubMed: 12077736]
- Williams E, Magid K, Steptoe A. The impact of time of waking and concurrent subjective stress on the cortisol response to awakening. *Psychoneuroendocrinology*. 2005; 30:139–148. [PubMed: 15471612]
- Wilson CJ, Finch CE, Cohen HJ. Cytokines and cognition--the case for a head- to-toe inflammatory paradigm. *Journal of the American Geriatrics Society*. 2002; 50:2041–2056. [PubMed: 12473019]
- Wright CE, Erblich J, Valdimarsdottir HB, Bovbjerg DH. Poor sleep the night before an experimental stressor predicts reduced NK cell mobilization and slowed recovery in healthy women. *Brain, Behavior, and Immunity*. 2006; 21:358–363.