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Sleep and Immunity: A Growing Field with Clinical Impact

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For millennia individuals have known that sleep is altered during sickness, and indeed many follow the advice to get sleep as an aid for recuperation from disease states. Hippocrates, more than 2400 years ago, made reference to the role sleep played in pathology. Yet systematic studies of sleep – immune interactions began just 30 years ago. During these past three decades, much progress has been made in our understanding of sleep – immune interactions during health and pathology.

Modern studies of sleep – immune interactions grew out of a subspecialty of endocrinology that focused on humoral regulation of sleep. Humoral theories of sleep posited that substances increased during waking, and when they reached some critical threshold, induced subsequent sleep. The first studies that directly tested these hypotheses were published in 1909 by Ishimori and in 1913 by Legendre and Pieron (Ishimori, 1909; Legendre and Piéron, 1910; Legendre and Piéron, 1913). These pioneering studies used the same approach: cerebrospinal fluid from sleep deprived dogs was injected into rested recipient dogs. The recipient dogs fell into a deep, narcosis-like sleep state. Although these findings were replicated in various ways during the next 60 years, e.g. Schnedorf and Ivy (Schnedorf and Ivy, 1939) and Borbely et al (Sachs et al., 1976), it was to take almost 80 years before likely candidates mediating these “hypnotoxin effects” were identified.

During the 1960s and 1970s, several groups were using this approach in an attempt to identify substances involved in sleep regulation. This type of research was by this time being referred to as “sleep factor research” and delta sleep inducing peptide (Schoenenberger et al., 1977) was the first to be identified. In the 1980's several additional substances, isolated from brains derived from sleep deprived animals were characterized, including uridine (Honda et al., 1984) and a muramyl peptide (Krueger et al., 1982). The latter finding provided a link between sleep and the immune system because it was known at the time that muramyl peptides were components of bacterial cell walls and induced the production of immune response modifiers.

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A direct connection between immunocytes and sleep was made by Akerstedt's group, which demonstrated that sleep loss led to altered phytohemagglutinin-stimulated lymphocyte DNA synthesis *in vitro* (Palmblad et al., 1979). Shortly thereafter, other investigators took the approach of characterizing the sleep-promoting actions (or wake-promoting actions) of known mediators of inflammation such as adenosine (Radulovacki et al., 1982) and prostaglandins (Haubrich et al., 1973; Laychock et al., 1980; Ueno et al., 1982), albeit this work was not framed within the context of a link between sleep and the immune system. These early studies set the stage by first demonstrating that sleep loss affected immunocyte function, and then that bacterial-derived substances alter sleep. As such, bi-directional interactions between sleep and the immune response were established. By 1983 (Krueger et al., 1983) interleukin-1 was linked to sleep regulation. This discovery led to the expansion of research relating sleep to host defense and the cytokine mechanisms involved. The topic of cytokines and sleep was the focus of an earlier special issue of *Brain, Behavior, and Immunity* (Opp, 2004).

The knowledge that bacterial-derived products altered sleep drove research focused on infection-induced alterations in sleep. In a series of studies, Toth and colleagues demonstrated the extent to which infection altered sleep of laboratory animals. Pathogens included Gram-positive and Gram-negative bacteria, viruses, fungi, and parasites [reviewed (Opp et al., 2007; Toth, 1999; Toth and Opp, 2002)]. Seminal studies by Norman also demonstrated the extent to which sleep of individuals infected with HIV was altered (Norman et al., 1992; Norman et al., 1990; Norman et al., 1988). Studies of HIV-induced alterations in sleep have since been conducted by many groups [reviewed (Toth and Opp, 2002)] and continues to be a topic of active research, as evidenced by the contribution of Lee et al., in this issue (Gay et al., 2014). Although it is clear that sleep is altered, the question of whether altered sleep during infection facilitates recovery remains. Some intriguing ecological studies of the energetic cost of fueling the immune system suggest a phylogenetic relationship between sleep duration and parasite load (Opp, 2009; Preston et al., 2009). A retrospective study by Toth suggests sleep patterns may be important to survival from infections, as rabbits with robust early sleep responses to infectious challenge have a better prognosis than rabbits with “poor sleep” responses during the course of infection (Toth et al., 1993). Collectively, data suggest sleep, as part of the acute phase response to infection may be beneficial for recovery, but definitive studies to test this hypothesis remain to be conducted.

Although much remains to be learned of mechanisms underlying sleep – immune interactions, and there are active research programs pursuing these goals, there is now increased effort focused on the relationship of sleep to pathologic conditions other than infection. Epidemiological studies consistently demonstrate associations between suboptimal sleep and chronic disease. The Center for Disease Control and Prevention uses multiple surveillance mechanisms to monitor many aspects of public health. The Behavior Risk Factor Surveillance System (BRFSS), a random-digital-dialing telephone survey that covers all 50 states, the District of Columbia, and US territories, annually includes more than 450,000 respondents. In addition to core questions about chronic disease and mental health, beginning in 2010 this survey includes an optional sleep module. In 2010, the sleep

module was administered in 14 states, and there were 54,269 respondents aged 45 or older included in analyses of sleep and chronic disease (Liu et al., 2013). Approximately 31% of respondents reported being short sleepers (≤ 6 h per night), 65% reported optimal sleep (7 – 9 h per night), and 4% indicated they were long sleepers (≥ 10 h per night). Although there are limitations inherent in cross sectional surveys, the adjusted model (controlling for age, sex, race/ethnicity, and education) revealed that suboptimal sleep (short or long sleep) was associated with increased odds ratios (OR) for obesity (OR 1.60), coronary heart disease (OR 1.92), stroke (OR 2.47), and diabetes (OR 1.83). The odds ratios diminish slightly in models controlling for obesity and frequent mental illness, but remain significant for each of the aforementioned diseases.

Another recent epidemiological study, the European Investigation into Cancer and Nutrition (EPIC)-Potsdam study (von Ruesten et al., 2012), gains relevance because it includes data with respect to suboptimal sleep and cancer risk. This longitudinal study reports data from 23,630 respondents who were followed, on average for almost 8 years. These data reveal that when stratified by age and adjusted for sex and many other variables, short sleep (< 6 h per 24 h period) is associated with overall chronic disease [hazard ratio (HR) of 1.31], including increased risk for stroke (HR 2.06), myocardial infarction (HR 1.44), and cancer (HR 1.43). Of interest, this study also reports that in non-hypertensive respondents the overall risk of chronic disease, primarily cancer, is reduced by a daytime nap. This study is the first to demonstrate a relationship between short sleep and overall cancer risk, although some studies suggest insufficient sleep may be associated with increased breast cancer risk (Kakizaki et al., 2008). The authors of the EPIC-Potsdam study conclude that sleep duration less than 6 h is a “risky behavior” for the development of chronic disease. These, and other studies [e.g., (Ayas et al., 2003; Cappuccio et al., 2011; Chen et al., 2008; Gangwisch et al., 2007; Mallon et al., 2005; Meisinger et al., 2007)] are critically important from a public health perspective as they emphasize that chronic suboptimal sleep is associated with chronic diseases that incur tremendous cost in terms of lives lost and burden to health care systems. Yet, epidemiological studies do not address mechanisms underlying suboptimal sleep as a risk factor for chronic disease. Perhaps the most important aspect of current research on sleep – immune interactions is effort focused on understanding the mechanisms by which suboptimal sleep leads to chronic disease.

It is now well-established that cytokines and their receptors are expressed in brain, where they function in multiple physiological processes and behavior. Many pro-inflammatory cytokines, including IL1 and TNF, are also pro-somnogenic, and conversely, anti-inflammatory cytokines (IL4, IL10, IL13, the IL1 receptor antagonist) are anti-somnogenic [reviewed (Krueger, 2008; Opp, 2005; Zielinski and Krueger, 2011)]. Because these cytokines, and other chemokines and growth factors, are involved in physiological sleep regulation/modulation, it is logical that disrupted sleep would alter their expression.

Within the context of this commentary is the current consensus within the sleep research community that sleep loss induces inflammation. Because the chronic diseases that plague our western civilization and are associated with suboptimal sleep are inflammatory diseases, it seems likely that chronic insufficient sleep is a risk factor, in part because of the inflammatory state that results from sleep disruption. Inflammation, defined by elevated

local and systemic cytokines and other pro-inflammatory mediators, occurs in response to many stimuli, including pathogen exposure, cellular damage, irritants, cellular dysregulation, and waking activity. Acute inflammation occurs on a time scale of seconds to days, allows the host to effectively heal and protect damaged tissue from disease, and resolves. Chronic inflammation does not resolve, and is linked to many pathologies and age-related diseases including, but not limited to sleep apnea, insomnia, neurodegeneration, Alzheimer's disease, atherosclerosis, cancer, kidney and lung diseases, metabolic syndrome, and type 2 diabetes mellitus.

Sleep, sleep loss and disrupted sleep are strongly linked to acute and chronic inflammation. Many studies of healthy human volunteers subjected to sleep restriction or sleep deprivation demonstrate changes in circulating pro-inflammatory and anti-inflammatory cytokines, soluble receptors, inflammatory signaling pathways, and innate immunity (Dinges et al., 1994; Haack et al., 2004; Haack et al., 2007; Irwin, 2002; Irwin et al., 2010; Irwin et al., 2006; Lekander et al., 2013; Meier-Ewert et al., 2004; Mullington et al., 2009; Mullington et al., 2010; Simpson and Dinges, 2007). Recent studies (Leproult et al., 2014), including two in this issue (Phillips et al., 2014; Wright, Jr. et al., 2015) demonstrate that circadian misalignment (during which sleep is disrupted), also induces inflammation, which has ramifications for shift workers. Indeed, shift work is a risk factor for, or associated with inflammatory disease, including cancer (Flynn-Evans et al., 2013; Rabstein et al., 2014; Sigurdardottir et al., 2013) and diabetes (Knutsson and Kempe, 2014; Monk and Buysse, 2013). Collectively, there is ample evidence that disrupting sleep alters multiple pathways in a manner that results in an inflammatory state. Regardless, our knowledge of the mechanisms underlying links between sleep and multiple facets of chronic disease remains incomplete. Contributions to this special issue of *Brain, Behavior and Immunity* demonstrate the breadth of research currently focused on the relationship of sleep and suboptimal sleep to chronic disease. These contributions expand our understanding of this underappreciated, understudied, yet critical component of immunity – sleep.

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