

## Sleep and Infectious Disease Risk

Commentary on Prather et al. Sleep and antibody response to hepatitis B vaccination. *SLEEP* 2012;35:1063-1069.

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Epidemiology studies have identified adverse social and environmental conditions such as death of a spouse, low socioeconomic status, or social isolation with increased risk of infectious disease (presumably due to insufficient immune gene expression), and with inflammation-associated cardiovascular, autoimmune, neurodegenerative, and neoplastic diseases (presumably due to excessive immune gene expression).<sup>1,2</sup> Efforts to understand the specific neurobehavioral pathways through which stressful life circumstance affect immune responses are needed to inform the development of targeted interventions that might ameliorate this disease risk profile.

Sleep-wake cycles have emerged as prominent regulators of the immune system. Experimental sleep restriction studies show that sleep amounts are associated with alterations in *ex vivo* measures of cellular immunity implicated in risk of infectious disease (e.g., natural killer cell activity, T-cell proliferative response)<sup>3-5</sup> and with upregulated leukocyte expression of pro-inflammatory cytokine genes, activation of the transcription factor nuclear factor (NF)- $\kappa$ B, and increased monocyte expression of inflammatory cytokines.<sup>6,7</sup> Observational studies have also identified associations between sleep disturbance, as found in night-shift workers or in those with insomnia, and alterations in cellular immune responses as well as biomarkers of inflammation.<sup>5,8</sup>

Translation of these observations of altered immune responses to clinically relevant endpoints related to infectious disease risk is needed. To this end, emerging evidence suggests that sleep impacts immunologic response to vaccination. Small-scale, experimental studies have found that timing of sleep deprivation with immunization leads to lower antibody titers in response to challenge with hepatitis A, hepatitis B, or influenza vaccine.<sup>9-11</sup>

In this issue of *SLEEP*, Prather and colleagues<sup>12</sup> have substantially extended these prior findings using a sample of 125 midlife adults and an observational prospective design, to provide robust evidence that amounts of sleep influence the magnitude of specific immune response to a novel viral antigen, hepatitis B. Furthermore, they show that shorter sleep duration (i.e., less than 6 hours per night) was associated with a decreased likelihood of clinical protection following hepatitis B vaccination, even after three doses of vaccine including a booster dose at 6 months. Importantly, sleep duration was assessed using both subjective and objective measures (e.g., actigraphy)

with similar convergent results. Moreover, these observations are consistent with other data from this investigative team using another infectious disease model, common cold infection.<sup>13</sup> In this prior study, Cohen et al. found that sleep-reported measures of poor sleep efficiency and shorter sleep duration were associated with increased susceptibility to the common cold virus following experimental inoculation with a rhinovirus.<sup>13</sup> Together, these observations demonstrate that variations in sleep duration that occur in the natural setting have the potential to impact infectious disease risk, in which short sleep duration acts not only to increase viral pathogen susceptibility or expression of symptoms, but also to decrease the immunologic protection offered by a standard clinical vaccine to hepatitis B. Whereas neither of these prior studies evaluated infection rates, epidemiologic data recently published in *SLEEP* have found that both reduced (e.g., < 5 h) and prolonged (e.g., > 9 h) habitual sleep durations are associated with increased risk of pneumonia.<sup>14</sup> Hence, to the extent that behavioral and pharmacologic treatments can improve short sleep duration, infectious disease risk profiles might be modifiable in those with insomnia or in older adults, who by virtue of their age have shorter sleep times and are more susceptible to viral infections and attenuated vaccine responses.

Why sleep contributes to these dynamic variations in the immune system and response to vaccine is subject to debate. However, we have previously speculated that the quiescent period of sleep serves to reallocate energy resources from functions related to wakefulness to processes that, for example, facilitate and promote immune responses to infectious challenge.<sup>8</sup> With the nocturnal movement of immune cells out of the circulatory system and possibly into the lymph nodes, naive T and B cells get their first exposure to foreign antigens and an adaptive immune response is initiated. Such responses that involve immune-cell division and differentiation require metabolic resources, and such metabolic demands can be more efficiently supported during sleep. Indeed, Lange et al.<sup>11</sup> recently found that high sleep slow wave activity during the night after vaccination promotes antiviral immune responses by facilitating the transfer of antigenic information from accessory cells to antigen specific T cells. In other words, the immune system takes advantage of the offline conditions during sleep to foster adaptive immune responses resulting in improved immunological memory.

Sleep loss is associated with a pattern of infectious- vs. inflammation-associated disease risk, and the signaling pathways that coordinate such divergent immune responses require consideration. Central nervous system (CNS) regulation of immune responses are primarily driven by two effector signaling pathways: activation of the hypothalamic pituitary adrenal (HPA) axis and the sympathetic nervous system (SNS).<sup>1</sup> Substantial evidence has shown that sleep loss activates sympathetic activ-

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ity, with less robust evidence of effects on the HPA axis.<sup>15</sup> Indeed, whereas activation of HPA axis inhibits both antiviral and pro-inflammatory genes, sympathetic nervous system activation suppresses antiviral responses while stimulating pro-inflammatory genes, which together provides a plausible mechanism to connect sleep disturbance with both infectious- and inflammatory disease risk.<sup>1</sup> The neural fibers of the SNS distribute the neurotransmitter norepinephrine into tissue microenvironments in which immune response gene transcription occurs, including all primary and secondary lymphoid organs, the vasculature and perivascular tissues, and most visceral organs and musculoskeletal structures. Initially,  $\beta$ -adrenergic signaling was found to modulate adaptive immune responses by stimulating transcription of T helper 2 (Th2)-type cytokine genes (such as *IL4* and *IL5*) and suppressing Th1-type gene expression (such as *IFNG* and *IL12B*). However, SNS-mediated steering of innate immune response programs also involves suppression of type I IFN-mediated antiviral responses and upregulated transcription of pro-inflammatory cytokines such as *IL1B*, *TNF*, and *IL6*.<sup>2</sup> Collectively, these studies of SNS regulation of inflammatory and antiviral genes also suggest the potential for neuropharmacological strategies for mitigating the observed effects of sleep disturbance on inflammatory and infectious disease outcomes.

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