EDITORIAL

Resisting Sleep Deprivation by Breaking the Link Between Sleep and Circadian Rhythms

Commentary on Arnardottir et al. Blood-gene expression reveals reduced circadian rhythmicity in individuals resistant to sleep deprivation. SLEEP 2014;37:1589-1600.

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While it is apparent that all humans suffer decreased performance on many cognitive tasks with sleep deprivation, there is tremendous inter-individual variability in the magnitude of the impairment.[1-3] The amount of impairment for each individual is specific to the type of cognitive task,[1-3] and only a minor proportion of the variability is explained by baseline task performance prior to sleep deprivation.[1] The amount of susceptibility is a trait-like feature of the individual, which appears to be heritable[4] and highly reproducible over time.[1,2,5] Despite efforts to identify physiological, behavioral or genetic determinants that modify the response to sleep deprivation, relatively little is known about the molecular mechanisms that underlie these individual differences.[5-7]

The goal of the study reported in this issue of *SLEEP* by Arnardottir, Nikonova, et al.[8] was to determine whether subjects that are differentially sensitive to the effects of sleep deprivation had differential gene expression patterns in blood. The authors selected 7 resistant and 7 sensitive subjects from a prior study,[4] based on their performance on the psychomotor vigilance test (PVT)[9] following acute total sleep deprivation. The PVT is a robust measure for this purpose because it tests for vigilant attention, which is particularly sensitive to sleep deprivation, and performance on the PVT is not influenced by subject aptitude, learning or psychometric bias.[10] Blood was sampled every 4 hours to measure gene expression using microarray during 24 hours of baseline sleep/wake assessment, 38 hours of continuous wakefulness (i.e., sleep deprivation), and a night of recovery sleep. The expression of 18,983 unique genes was measured at 19 time points for each subject, producing a large and comprehensive dataset of gene expression changes over time. Gene expression changes were compared between the sensitive and resistant subjects at baseline, after sleep deprivation and during recovery. The sensitive and resistant subjects had no difference in PVT performance or gene expression patterns under normal sleep/wake conditions, and both groups made increased PVT lapses with sleep deprivation, but as expected, the magnitude of these lapses was significantly greater in the group of sensitive subjects.

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Surprisingly, very few genes altered their expression in a state-specific or linear fashion as a result of sleep deprivation. Previous studies have also only found a limited number of gene expression changes in blood during sleep deprivation, and the magnitude of the expression change is small and variable,[11,12] even within an individual, suggesting that these findings are subjected to a large degree of statistical noise. Importantly, there were no differences in state-specific or linear gene expression changes between the sensitive and resistant subject groups. Taken together, these data argue that in humans there is not a straightforward gene expression response to sleep deprivation that explains the differential susceptibility between subjects, at least when gene expression is measured in pooled blood cells. The identification of a universal molecular signature (a gene or set of genes) of differential susceptibility will be challenging, especially given the mixture of cell types in blood, differences in expression patterns in the nervous system vs the periphery, the impact of stress on gene expression profiles after sleep deprivation,[13] and the fact that inter-individual differences in sleep deprivation-induced deficits are task-specific,[1-3] rather than global individual-specific deficits.

However, differences between the resistant and susceptible groups became apparent when the authors looked at changes to the daily pattern of gene expression. During normal sleep/wake, they found 4,481 unique genes (23.6% of the genes they assessed) with a significant 24-h rhythm in expression pattern. Based on an important prior finding that sleep restriction causes a reduction in the number of genes with a circadian expression profile,[11] the authors specifically compared the expression profile of the rhythmic genes. Resistant subjects had a significant reduction in the amplitude of the daily expression pattern, resulting in a reduced number of genes with a significant rhythmic expression profile, while sensitive subjects had no change in the amplitude or number of rhythmically expressed genes during sleep deprivation.

This finding suggests that behaviorally resistant subjects were able to respond to extended wakefulness by significantly dampening oscillating expression patterns. Subjects that were behaviorally sensitive appear to suffer a transcriptional resistance to the changed internal milieu; they failed to make the necessary molecular adaptations, and continued to express genes in a daily fashion as though they were still on a normal sleep/wake cycle. A recent elegant study showed that desynchrony between sleep and circadian phase (i.e., mistimed sleep) also dampens the amplitude of rhythmic changes in blood gene expression.[14] While circadian regulation of the transcriptome

allows for specialized cellular functions to optimally match time of day and sleep/wake state, this specialization likely impairs vigilance quality and cognitive functioning when it orchestrates specific cellular, molecular and metabolic processes to occur during sleep. Turning down this specialization (i.e., dampening the circadian regulation to better maintain the "waking molecular signature") may be advantageous in unanticipated sleep/wake states and individuals resistant to sleep deprivation may be able to do this more efficiently than sensitive individuals.

At the moment the relationship between a dampened circadian rhythm in gene expression and resistance to sleep loss is only correlational. Testing whether enhancing or dampening circadian rhythmicity of the transcriptome will produce changes in neurobehavioral impairments after sleep deprivation in model systems is required. In addition, the role of specific genes in this process remains unclear. The authors looked specifically at changes in the core clock genes and found no differences at baseline, but did not report on the potential difference between sensitive and resistant subjects in clock gene expression amplitude after sleep deprivation. These molecular elements are attractive candidates because of their role in sleep homeostasis[15,16] and in modulating the sensitivity to sleep deprivation.[17-19] Expression data from this study will be publically available and can be revisited to identify potential candidate genes and importantly, validate these microarray results with replication and qPCR. Screening for genes involved in epigenetic regulation would also be interesting because they are known to respond to sleep timing[14] and sleep deprivation,[20] and play major roles in regulating gene expression and cognitive function.

CITATION

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DISCLOSURE STATEMENT

The authors have indicated no financial conflicts of interest.

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