COMMENTARY

Locus Coeruleus Neural Fatigue: A Potential Mechanism for Cognitive Impairment during Sleep Deprivation

Commentary on Bellesi et al. Region-specific dissociation between cortical noradrenaline levels and the sleep/wake cycle. *SLEEP* 2016;39(1):143–154.

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Noradrenaline (NA) is an important neuromodulator involved in many aspects of behavior including wakefulness, response to novelty, attention, and stress.[1–4] NA is primarily produced by the locus coeruleus (LC) and LC neurons project widely throughout the brain including the cortex.[5] LC neurons exhibit state dependent firing patterns with low tonic firing rates during wakefulness punctuated by increased phasic activity during salient stimuli, decreased tonic activity during NREM sleep and near silence during REM sleep.[6] Sleep is critical to maintain health[7] and sleep deprivation leads to many negative health consequences. These include lowered immune function,[8] metabolic dysregulation,[9] and impaired cognitive performance,[10] yet the mechanisms that lead to these deficits remain unclear.

In this issue of *SLEEP*, Bellesi and colleagues[11] identify one potential mechanism by which prolonged wakefulness can lead to cognitive decline. This is the first study to measure dynamic changes in NA levels in the mouse cortex using *in vivo* microdialysis during prolonged wakefulness. Bellesi found that absolute levels of NA were higher in the medial prefrontal cortex (PFC) versus primary motor cortex (M1). NA levels increased with prolonged wakefulness and decreased during sleep in both regions but the dynamics were faster in M1. In PFC, but not M1, NA levels started to decline after extended prolonged wakefulness. This suggests that LC neurons projecting to PFC are not able to maintain NA release for long periods of time. Synaptic fatigue may be due to NA synaptic vesicle depletion with sustained activity and is consistent with findings from Carter et al.,[12] where extended LC firing at 10 Hz for 10 min resulted in decreased NA levels in the PFC. The differences in NE responses to sleep deprivation between PFC and M1 suggest that those projections originate from different populations of neurons within the LC and that individual populations of neurons within the LC are differentially susceptible to fatigue. The PFC projecting LC neurons susceptibility to fatigue may also be due to an inherent higher firing rate of PFC projecting LC neurons over M1 projecting LC neurons.[5] Interestingly, M1 NA was correlated with both motor activity and the number of novel objects presented during sleep deprivation, whereas PFC NA was only correlated with the number of novel objects presented. These findings are consistent with the role of M1 in motor activity and PFC in attention.[13] As the authors mention, these findings fit with observations that motor activity is the least susceptible to sleep deprivation, whereas cognitive functions are very susceptible to sleep deprivation.[14]

This study by Bellesi et al.[11] represents an important first step at understanding neural fatigue with prolonged wakefulness. Two challenges of sleep deprivation methods include minimizing stress and controlling for increased locomotion.[15] In this study, the two brain regions studied relate specifically to attention (PFC) and locomotor activity (M1) and are potentially sensitive to the method chosen for sleep deprivation. Baseline waking NA levels were collected while mice were on a slowly-rotating platform for 2 h, during which time NA levels were stable in both PFC and M1. Following these waking baseline measures, groups of mice were permitted spontaneous sleep-waking for 6 h or subjected to sleep deprivation for 6 h using introduction of novel objects. Prolonged wakefulness with novel objects induced an initial increase in NA in both PFC and M1 but only the PFC NA levels declined at the end of sleep deprivation. The authors suggest that the moving platform induced stereotyped behaviors leading to stable waking levels in NA, whereas introduction of novel objects lead to varying levels of attention thus increased NA. Therefore, the novel object method of sleep deprivation may preferentially activate LC to PFC neurons over LC to M1 neurons. Sleep used to be thought of as a whole brain phenomenon but recent evidence suggests that sleep can occur locally and is more intense in brain regions that experience greater use during wakefulness.[16] Therefore, one explanation for the differential responses of NA levels in PFC versus M1 is that PFC was more active than M1 in the novel object sleep deprivation paradigm. It would be interesting to see if using other methods of prolonged sleep deprivation that do not specifically increase attention, like the moving platform, would produce the same increase in NE and selective fatigue of LC to PFC neurons.

Microdialysis is an excellent technique for long term monitoring of in vivo neurotransmitter levels but has low temporal resolution compared to electrochemical biosensors like cyclic voltammetry.[17] Therefore, future studies using methods with faster sampling rates are needed to refine our understanding of the temporal resolution of NA changes across the short epoch duration and rapid transitions between sleep and wake observed in rodents. In the present study, NA did not correlate with slow wave activity, a measure of sleep pressure, in either brain region. This lack of correlation could be due to the long sampling rate of microdialysis compared to the faster sampling rate of the electroencephalogram. Additionally, new techniques like optogenetics[18] that allow for selective activation of specific LC projections to either the PFC or M1 will help define their respective functions. For example, would activation of LC to PFC projections drive wakefulness or attention more or less than activation of LC to M1 projections?

Overall, Bellesi et al.[11] identify one possible mechanism by which sleep deprivation leads to cognitive impairment. The

decrease in PFC NA with prolonged wakefulness, presumably due to neural fatigue, may be one part of the complex network that leads to increased sleep pressure via withdrawal of an arousal signal. Interestingly, neural fatigue seems to be specific to PFC projecting LC neurons as compared to other projections of LC and other components of the arousal system like orexin,[19] histamine,[20] serotonin, or dopamine,[21] which do not fatigue with prolonged wakefulness. Staying awake is so important evolutionarily, that there are multiple neural circuits that promote overall arousal. However, each individual brain region may contribute differentially to components of arousal. An exciting relevant application of this study's findings to clinical sleep diagnostics is the observation that pupillary size instability, which is controlled by the LC,[22] increases with prolonged wakefulness,[23] and may be a good biomarker of sleepiness.

CITATION

Van Dort CJ. Locus coeruleus neural fatigue: a potential mechanism for cognitive impairment during sleep deprivation. *SLEEP* 2016;39(1):11–12.

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ACKNOWLEDGMENTS

The author thanks Mohsen Hozan for helpful comments and discussions in preparing this manuscript.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication October, 2015
Accepted for publication October, 2015
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DISCLOSURE STATEMENT

Dr. Van Dort has indicated no financial conflicts of interest.