The sleep-deprived hippocampus: a loss in translation

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Submitted 21 November 2012; accepted in final form 21 November 2012

IT IS TAKEN FOR GRANTED by the scientific and lay communities alike that sleep is a profoundly important physiological process. Yet, because sleep encompasses a constellation of physiological and biochemical changes, ascertaining the function(s) of sleep is a challenge that has vexed inquiring minds for ages. In the past couple of decades, the emergence of large-scale screening techniques for detecting molecular consequences of sleep and sleep loss has helped to define our thinking. There is now a strong and reliable link between sleep changes and the expression of molecular markers for synaptic plasticity (2). Vecsey and colleagues (9), in the laboratory of Ted Abel, report that sleep deprivation suppresses a subset of insulin receptor-responsive pathways in the cell, including the mammalian target of rapamycin (mTOR), a translational regulatory protein. Collectively, with recent observations by Seibt and colleagues (7) in the laboratory of Marcos Frank, these observations help to identify a molecular switch linking sleep loss to both synaptic plasticity and cerebral metabolism in one fell swoop. In both the cerebral cortex (7) and the hippocampus (9), the translational regulatory pathway centered on mTOR is modulated as a function of sleep and sleep loss.

The Vecsey et al. (9) study began with a microarray analysis of gene expression in the hippocampi of sleep-deprived and spontaneously sleeping control mice. Of 22,689 probe sets measured by microarray, 2.7%, corresponding to a total of 533 genes, were differentially expressed in the hippocampi of sleep-deprived vs. control mice. A subset of these changes was verified by real-time PCR, with 18 of 19 real-time experiments confirming the microarray results (and the 19th trending in the same direction as the microarray data but not reaching statistical significance). The Database for Annotation, Visualization, and Integrated Discovery (DAVID) was then used to identify, in the microarray data, clusters of functionally related genes that were up- or downregulated in concert. One theme that was common among downregulated transcripts was molecular biosynthesis: transcripts that function in the processing of RNAs and proteins (including their intersection, translation) were common among those downregulated. This observation, coupled with the observed upregulation of the translation inhibiting unfolded protein response, led the authors to hypothesize that sleep loss leads to suppression of protein synthesis. Among the protein synthesis-supporting mechanisms downregulated in response to sleep loss, according to their analysis, was the insulin-responsive mTOR signaling pathway. This contention was supported by Western blots, which showed reductions in both total mTOR protein and phosphorylated mTOR protein in the hippocampus, as a consequence of sleep loss.

So what does downregulation of mTOR due to sleep loss tell us about the function(s) of sleep? Protein synthesis is a metabolic burden on the cell. There are mechanisms in place to assure that protein synthesis occurs only when the cell has sufficient energetic resources to support the process, and mTOR is central to this regulatory regime (4). mTOR promotes translation as a function of cellular energetic status. Insulin signaling, which is indicative of a glucose-rich (i.e., energetically endowed) environment activates mTOR. Conversely, adenosine monophosphate (AMP)-activated protein kinase (AMPK) activity inhibits mTOR in response to depletion of the cellular energetic currency, ATP. This arrangement allows for activation of protein synthesis when energy is plentiful and suppression of protein synthesis when energy is scarce (3). So the data from Vecsey and colleagues provide, in the form of downregulation of mTOR during sleep deprivation, an indication that sleep loss represents a cellular energetic challenge. The energetic burden associated with sustained wakefulness obligates the suppression of mTOR-dependent translation. Sleep presumably reverses the energetic burden associated with neuronal activity during wake, allowing for diversion of resources into mTOR-dependent protein synthesis.

This report is not the first indication that sleep loss poses an energetic challenge to the brain. AMPK becomes phosphorylated and increases its kinase activity in response to cellular energetic challenge. Phospho-AMPK is elevated in the basal forebrain of sleep-deprived animals relative to spontaneously sleeping animals, and a similar trend exists in the frontal cortex (1). This observation, in addition to yielding biochemical validation that sleep loss represents a cellular energetic challenge, provides a transcription-independent mechanism by which mTOR activity, and with it protein synthesis, may be downregulated under conditions of sleep deprivation. The suppression of mTOR activity by AMPK during sustained wake may complement the suppression of gene expression in translation-promoting pathways. A follow-up study might measure phospho-AMPK and use pharmacological manipulations of AMPK activity in the hippocampi of sleep-deprived and control rats to address this hypothesis. Additionally, measurements of mTOR activity in the basal forebrain of sleep-deprived and control animals, where AMPK phosphorylation in response to sleep loss is particularly robust (1), would help to test this line of reasoning.

One could also augment the observations of Vecsey and colleagues (9) with pharmacological experiments to further hammer out the consequences of mTOR modulation by sleep. Pharmacological tools that modulate mTOR activity, including the very namesake of mTOR, rapamycin, might be administered to the hippocampi of sleep-deprived and spontaneously sleeping animals. If mTOR is in fact a key regulator of sleep...
loss and sleep homeostasis, then manipulating this regulatory pathway should have a profound impact on sleep-related plasticity in the hippocampus. This is already known to be the case in the cerebral cortex, where [as mentioned in the DISCUSSION by Vecsey and colleagues (9)] mTOR signaling is essential for sleep-dependent synaptic plasticity. This fact is demonstrated by the work of Seibt and colleagues (7). Six hours of monocular deprivation during wake results in ocular dominance plasticity (ODP), in which neurons formerly responsive to optical stimulation of the deprived eye become more responsive to the nondeprived eye. ODP can be detected at the end of a 6-h spontaneous sleep phase immediately after the 6-h waking monocular deprivation phase; but if sleep is prevented during this 6-h consolidation period, ODP fails to consolidate and is abolished. Knowing that sleep facilitates protein synthesis (6), Seibt and colleagues (7) sought to determine whether mTOR-dependent protein synthesis mediates sleep-dependent consolidation of ODP. They used intracortical infusion of rapamycin to inhibit mTOR-dependent translation. When infusion was done during 6 h of wake with monocular deprivation, expression of ocular dominance plasticity at the end of that 6-h interval was unaffected by rapamycin. However, when the intracortical infusion of rapamycin was done during 6 h of spontaneous sleep after 6 h of wake with monocular deprivation, expression of ODP at the end of that 6-h spontaneous sleep interval was blocked. Seibt and colleagues (7) concluded that sleep-dependent, mTOR-driven protein synthesis underlies the consolidation of ODP. Given this observation and the well-documented dependence of neural plasticity on mTOR (5), a powerful case can be made that mTOR is a key mediator of sleep-dependent plasticity.

These two reports suggest collectively that facilitation of mTOR-dependent protein synthesis by sleep may be a general property of laminar forebrain structures. But to what extent are changes in insulin-responsive and translation-related gene expression as a consequence of sleep deprivation reliable in the hippocampus and generalizable to other brain regions? A wealth of data on the macromolecular response to sleep deprivation is publically available. Informatic approaches will have to be applied to these databases to address the question.

Finally, the paper by Vecsey and colleagues (9) also provides fodder for another theme in sleep research, the link between sleep and cerebral energetics. While mTOR functions in plasticity, in fact, this molecule was originally characterized in the context of cellular metabolism, where it serves as a regulator of glucose utilization via glycolysis (8). This role for mTOR is not incompatible with its role in synaptic homeostasis. Indeed, mTOR may serve as a nexus for the integration of cellular glucose demand and synaptic activity, with changes in excitability and/or synaptic strength obligating shifts in the neuron’s processing of glucose and protein synthesis. It is posited that plastic events during sleep serve to reduce the overall excitability, and with it the metabolic demand, of the brain (2). mTOR may provide a molecular mechanism for this process. These are intriguing possibilities, and we have the work of Vecsey and colleagues (9) and the complementary work of Seibt and colleagues (7) to call them to our attention.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS
Author contributions: J.P.W. drafted manuscript; J.P.W. edited and revised manuscript; J.P.W. approved final version of manuscript.

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