NEUROSCIENCE

The molecular neurobiology of the sleep-deprived, fuzzy brain

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Sleep deprivation is well established to cause diminution of cognitive function, including disruption of both minute-to-minute working memory and decrements in the stabilization of long-term memories. Moreover, "replay" during sleep of episodes and sequences of events that were experienced during wakefulness has been implicated in consolidation of long-term memories. However, the molecular mechanisms underlying the role of sleep in memory function are just starting to be defined. In this issue of *Science Signaling*, Tudor *et al.* identify one molecular component underlying the effects of sleep on memory function: dynamic experience-dependent regulation of protein synthesis in the hippocampus.

We've all experienced it, whether cramming for exams, having new babies, taking long road trips, dealing with stress, or hearing noisy neighbors: sleep deprivation…and the attendant "fuzzy" head that comes along with it—lowered cognitive power, the loss of mental sharpness in working memory, and decreased capacity for remembering the facts and events of the day. Sleepless nights leading to fuzzy-headedness and blunted recollections is a universal human experience, so much so that it is the stuff of clichés and movie plotlines. We so much take for granted that it will happen that we never wonder why it happens. But a universal human experience such as this must be rooted in neurobiology, with an underlying cellular and molecular mechanism. Tudor *et al.* address this question in the current issue of *Science Signaling*. In their work, they awaken us to the fact that the effects of sleep on memory consolidation are subserved, in part at least, by a concise molecular signaling cascade regulating protein synthesis in response to the day's experiences.

Sleep is a mysterious process, and its complexity makes studying sleep-associated effects on memory difficult (*1*). Nevertheless, a number of studies demonstrate the importance of sleep-associated neuronal activity in memory consolidation, the processes that stabilize and store information within the hippocampus for eventual downloading to the cortex. Many investigators observed the reproduction of specific patterns of hippocampal pyramidal neuron firing during sleep that mimic firing patterns the animal had established while awake and learning [a review is available in (*2*)]. In other words, it seems the hippocampus and cortex are "replaying" events during sleep as a part of the process of memory consolidation. Indeed, a number of supporting studies suggest that removing these replay episodes causes memory dysfunction.

In considering what molecular processes might play a role in the sleep/memory interaction, it is important to note that protein synthesis has been implicated in memory consolidation since the 1960s, when Flexner and colleagues determined that administering a protein synthesis inhibitor at the time of training disrupts memory (*3*). Many investigators replicated these findings (*4*), with multiple activity-dependent regulators of protein synthesis emerging, including the insulin signaling pathway explored by Tudor *et al.* (*5*). Target of rapamycin (TOR) proteins are kinases that can interact with the regulatory-associated protein of mammalian TOR (mTOR) (raptor) to form the mTOR complex 1 (mTORC1) (Fig. 1). Of course, protein synthesis must begin with the recognition of an mRNA by the ribosomal complex. One mechanism for translational initiation involves the eukaryotic translation initiation factors 4E and 4G (eIF4E and eIF4G). In the brain, eIF4E is sequestered by the eukaryotic initiation factor 4E binding protein 2 (4EBP2). The mTORC1 complex phosphorylates 4EBP2, causing the release of eIF4E and allowing for subsequent binding to eIF4G and recruitment of mRNA to ribosomes for translation. Previously, Abel's group performed a genome-wide analysis to determine the effects of sleep deprivation on gene expression and revealed that 5 hours of sleep deprivation reduces the levels of mTOR in the hippocampus (*6*). However, the downstream effects of reduced mTOR on signaling and protein synthesis and the molecular mechanisms of sleep deprivation in vivo remained a mystery.

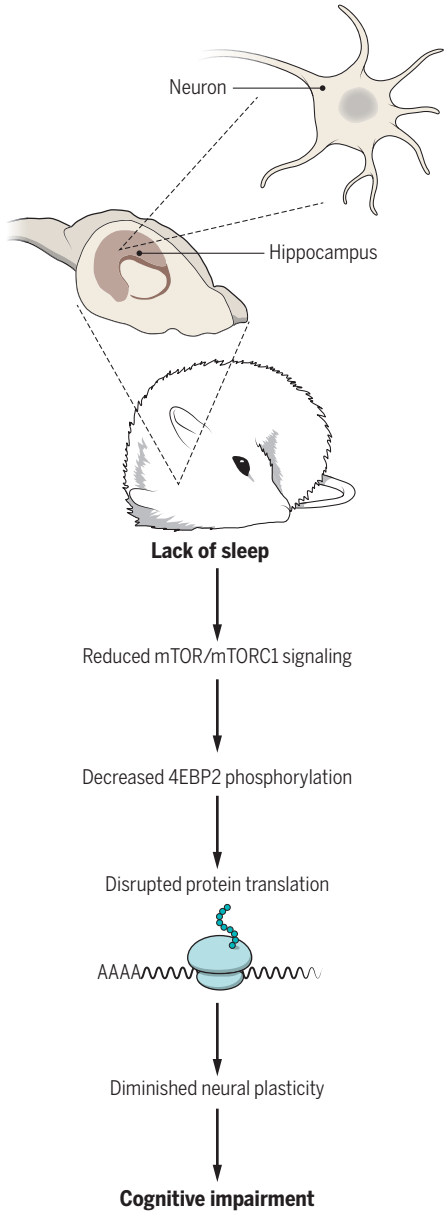

Fig. 1. Effects of sleep deprivation on protein synthesis via disrupted mTORC1 signaling. Reduced mTOR/mTORC1 signaling in hippocampal neurons of sleep-deprived mice leads to decreased phosphorylation of 4EBP2, resulting in disrupted protein translation, diminished neural plasticity, and ultimately, cognitive impairment.

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In this issue of *Science Signaling*, Tudor, Abel, and colleagues describe the results of a series of experiments that investigated the molecular signaling underlying sleep deprivation–induced impairments in hippocampus-dependent memory. The authors show that 5 hours of sleep loss reduces the activity of a core regulator of protein synthesis in neurons—specifically, mTORC1 signaling to 4EBP2 and, subsequently, the protein synthesis apparatus (Fig. 1). The authors demonstrate experimentally that increasing the expression of 4EBP2 in hippocampal excitatory neurons during sleep deprivation is sufficient to restore normal levels of protein synthesis and prevents memory loss induced by sleep loss. The authors are thereby able to convincingly conclude that mTORC1-4EBP2–regulated protein synthesis is a critical molecular signaling mechanism that mediates memory deficits induced by lack of sleep.

The findings are novel, the story is concise and convincing, and the data are presented clearly. However, there are a couple of issues that should be kept in mind. First, the conclusion is well supported in that their results demonstrate that sleep deprivation reduces protein synthesis in the hippocampus, but alternative mechanisms might be considered. The lack of an increase in the protein levels of these transcripts could be due to a decrease in mRNA stability or some mechanism other than, for example, the change in mTORC1-dependent translational control. Second, the authors observe that 5 hours of sleep loss decrease both mTORC1-mediated phosphorylation of 4EBP2 and the interaction of eIF4E and eIF4G. This is strong and direct evidence for an involvement of these processes, but the observation is still correlative in nature. The authors nicely showed that increased 4EBP2 expression in hippocampal pyramidal neurons restored the eIF4E–eIF4G interaction and rescued both protein synthesis and memory function after sleep loss, which rigorously tests several predictions of their model and are consistent with their interpretation. However, the complexity of the regulation of protein synthesis in the central nervous system is such that alternative parallel mechanisms might also be in play with sleep deprivation–induced fuzzy brain, as well.

Nevertheless, the authors have placed our understanding of the molecular neurobiology of sleep deprivation and its deleterious effects on memory cognition on a firm foundation. They present a pioneering insight into a universal human attribute, just as the best studies in the field of molecular and cellular cognition should do. Just be careful not to lose any sleep over it.

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