Sleep on it
Evidence of sleep-induced weakening of synapses lends support for a controversial hypothesis

By Graham H. Diering

Despite the fact that humans spend a large part of their lives engaged in sleep, we still do not know why. This question may be one of the most profound problems still facing neurobiology.

Sleep likely serves multiple important functions, but it is certain that it is critical to support higher cognitive processes such as learning and memory. The informational capacity of a human brain is vast, but the daily ability to incorporate new information may be finite. The restorative functions of sleep renew our capacity to incorporate new information, while at the same time allowing for the consolidation of long-term memory, incorporating our daily learning with our previous experiences.

In addition to asking why we sleep, we might also ask what actually changes in our brains while asleep? Because we know that it benefits learning and memory, at least one major target of sleep will likely be neuronal synapses, the sites of memory formation and maintenance. In work performed over recent years, I and my colleagues have attempted to gain a comprehensive picture of how synapses were altered during sleep and have begun the process of elucidating the molecular mechanisms driving these changes.

Synapses in the brain can change in both strength and number in a process called synaptic plasticity. Long-term potentiation and long-term depression (LTP and LTD, respectively) are widely believed to form the basis of learning and memory.

Neurons can also express a form of synaptic plasticity called homeostatic scaling, whereby a neuron simultaneously strengthens (scaling-up) or weakens (scaling-down) all of its synapses in a uniform direction. Since the first observation of this phenomenon was made by Gina Turrigiano in 1998 (1), homeostatic scaling has been almost entirely investigated in vitro. During this time, many of the underlying molecular mechanisms have been described. However, one critical question remains: When do neurons in a living animal actually use homeostatic scaling?

A controversial model of how sleep alters the brain to benefit cognition has emerged called the “sleep homeostasis hypothesis” (SHY), championed by Chiara Cirelli and Giulio Tononi. SHY posits that synapses are strengthened when we are awake because they are encoding our daily experiences, predominantly through LTP. This is offset during sleep by a global weakening of synapses that restores synaptic strength to basal states (2). Meanwhile, some memories are consolidated, whereas others are erased.

I believe that homeostatic scaling-down in cultured neurons is the best model we have for understanding the global weakening of synapses during sleep. Therefore, to understand how sleep modifies synapses, I dissected the brains of mice that were awake or had been sleeping and then used biochemical fractionation to isolate the postsynaptic density (PSD), a fraction highly enriched with synaptic material.

My first question was how many of the changes that had been previously observed during homeostatic scaling-down could also be seen in synapses from a sleeping mouse? The similarities were remarkable. In particular, sleep and scaling-down involved a reduction in synaptic levels of AMPA-type glutamate receptors, major excitatory transmitter receptors in the brain (3). This finding is consistent with SHY; strongly suggesting that synapses across the brain become weaker during sleep.

To gain a more comprehensive picture of how synapses were modified during sleep, we used quantitative proteomics to examine the PSD samples. Our results indicated that a full 20% of the synapse proteome was altered in the samples taken from sleeping mice, as compared with samples taken from mice that were awake, showing that profound changes were occurring at synapses throughout the brain during sleep.

This data set gave us a “parts list” of molecules regulated by sleep that is already helping us understand the molecular mechanisms that drive sleep-dependent remodeling of synapses.

In cultured neurons, one of the clusters of signaling molecules that was removed from synapses during sleep is regulated by a protein called Homer1a, which is expressed when neurons become highly active and initiates the homeostatic scaling-down response. Interestingly, the Homer1a protein was targeted to synapses in mice during sleep (3).

In further experiments, I determined that the targeting of Homer1a to synapses was highly sensitive to chemicals in the brain that mediate arousal and sleepiness (3). Noradrenaline, for example, which is strongly associated with an alert awake brain, prevented Homer1a from entering the synapse.

Adenosine, which builds up in our brains while we are awake and causes sleepiness as it accumulates, promoted the targeting of Homer1a to synapses. These findings led me to believe that Homer1a serves as an integrator of arousal and sleep need.

I therefore hypothesize that when we are fully aroused and awake, the brain’s ability to strengthen synapses and encode information from our experiences is maximized as noradrenaline blocks Homer1a access to synapses and prevents scaling-down. After a long day, synapses have become stronger and we begin to grow tired. Adenosine accumulated in our brains during this period will promote Homer1a targeting to synapses to initiate scaling-down and synapse weakening. An important element of this model is that Homer1a protein is expected to be expressed at higher levels in neurons that were the most active and engaged in learning during the wakening state, and these neurons will be the ones that benefit the most from the restorative process of scaling-down while asleep.

When faced with a challenging intellectual problem, ancient wisdom tells us to “sleep on it”; all will become clearer in the morning. It may be that there is a bit of molecular truth to this old adage. With continuing work, we can gain further insights into why we sleep and how sleep actually works to enable cognitive functions such as learning and memory.

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Graham H. Diering

Graham Diering received his bachelor’s and doctorate degrees at the University of British Columbia. As a postdoc at Johns Hopkins University, he characterized changes in synapse composition that occur during sleep. He is now an assistant professor at the University of North Carolina, Chapel Hill; his laboratory focuses on the role of sleep in neural development.
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