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Sleep: hitting the reset button

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Abstract

Many aspects of sleep, including the how and why, are still mysterious, especially its relationship to learning and memory. A new study suggests that sleep may serve to reset synaptic potentiation, linking it to homeostatic plasticity.

How and why do we spend a third of our lives asleep, and why do even fruit flies do it? Although we have all experienced the poor performance that accompanies inadequate sleep, many aspects of sleep remain mysterious, or at the very least controversial. In this issue, Vyazovskiy *et al.* [1] provide support for a synaptic view of sleep: namely, that it serves to enforce global homeostatic control of synapse strength, correcting the imbalances created during wakefulness (Fig. 1).

An important aspect of the 'how' is identifying what substance homeostatically regulates sleep, which is inferred from indirect experiments. Brain molecules that promote sleep should increase in concentration as a function of wake time. A substance that inhibits sleep and then decreases in concentration is equally viable in almost all cases. Adenosine is a good homeostatic candidate in mammals, but it may not be unique, and its role is also controversial[2]. Therefore, mechanisms of sleep drive are still wide open.

The 'why' asks what is the function of sleep? There are many possibilities, some of which are not mutually exclusive, such as maintaining metabolism (ATP replenishment) or enhancing cognitive performance. The latter idea is based on experiments documenting the improvement in learning and memory that accompanies a night of sleep[3], or even a nap[4], relative to sleep deprivation. The depth of slow-wave sleep in discrete brain regions increases as a function of cognitive load (or use) during the prior wake episode[5]. Even external (transcranial magnetic) stimulation of a brain region leads to an increased amplitude of slow-wave sleep specifically in that region during the subsequent sleep episode[6]. However, none of these studies address why these regions or circuits sleep. What is sleep for, and what happens during sleep? One popular idea is that long-term memory is enhanced during sleep, as newly learned tasks or percepts are transitioned from short-term storage[3]. This should require more synapses and/or synapse strengthening, at least in those circuits associated with the newly learned task. Another idea is that most new information is discarded during sleep, as diurnal animals are bombarded by stimuli during the day, most of which we want to (or need to) forget. If this is the dominant reason why we sleep, then decreased numbers of synapses or synapse weakening should be a prominent neuronal feature of sleep.

The concept of homeostasis, maintaining a system at a particular set point using feedback modulation, is an old one. More recently, the idea that neurons and neural networks exhibit homeostatic regulation has become an important partner to Hebbian learning rules[7]. Homeostatic plasticity can take many forms, with the regulated set point involving relative synaptic strength, neuronal excitability and/or firing rate. It can also be expressed either pre- or postsynaptically. This broad view of homeostatic plasticity is relevant to the main thrust of the study by Vyazovskiy *et al.*[1], which shows consistent correlations between molecular and

electrophysiological markers of synaptic strength during the early phases of sleep and in wakefulness. Wakefulness increases net potentiation, which is then reduced during recovery sleep. This ensures that the potentiation process can begin anew during the next wake episode.

Plasticity in excitatory neurons of both the cortex and hippocampus is associated with alterations in the activity of signal transduction molecules and synaptic glutamate receptor levels. AMPA receptors of the GluR1 class are believed to be key determinants of synaptic strength. Their cell surface levels and phosphorylation state are altered by activity, with changes in AMPA receptor levels leading to changes in NMDA receptor levels. Potentiation involves trafficking of GluR1 from internal stores to synaptic sites, whereas depotentiation is associated with their removal from the synapse[8].

Using antibodies specific for synaptic proteins, and for particular phosphorylated sites on these proteins, Vyazovskiy *et al.*[1] demonstrate that the levels of these markers in a synaptoneurosome preparation correlate with the amount of sleep the animal had in the 6 h before it was killed. Rats were assigned to the sleep group if there was polysomnographic evidence of at least 4 h of sleep in that period; animals that had at least 4 h in a waking state were assigned to the wake group. Sleep-group animals had a small, but statistically significant, decrease in the amount of GluR1, as well as a significant shift in its phosphorylation into a depotentiated form. Wake-group animals showed upregulation of GluR1 and NR2A, as well as a change in GluR1 phosphorylation that was consistent with potentiation. CaMKII and glycogen synthase kinase–3 also showed changes that correlated with sleep state. Although total kinase levels were not changed, the amount of activated kinase, which is associated with potentiation, increased in the wake-group animals. Similar changes in these biochemical markers were seen when a prolonged wake state was induced during the light period by engaging animals with novel objects to prevent them from sleeping.

Plasticity is also associated with alterations in the electrophysiological properties of brain tissue. One commonly used measure of synaptic strength is the slope of evoked local field potentials (LFPs), which increases with the net potentiation of a neuronal population responding to a stimulus and decreases with the net depotentiation. Measurements were made by stimulating one side of the cortex and recording from the other, with the idea being that the first downward deflection would be a monosynaptic transcallosal response. Potentiation correlated with waking and scaled with the amount of time spent awake (either spontaneously or stimulated by providing novel toys in the cage) before the LFP measurement. Although this might reflect the acute behavioral state of the animal rather than its sleep history, the authors used polysomnography, electromyograms and observation to show that the slope did not correlate with what the animal was doing at the moment of measurement, but rather with the amount of sleep or waking in the several hours preceding the recording. Slow-wave activity, a measure of sleep drive, was also weakly correlated with LFP slope, consistent with synaptic strength changes scaling with prior sleep history. As predicted from these gross changes in potentiation, the ability to induce cortical LTP was partially occluded in animals that had been awake. Sleep before induction, however, allowed a low level of stable LTP to form. Although many of these changes were subtle, they were statistically significant and argue for a role for sleep in the homeostatic resetting of net synaptic strengths.

The findings by Vyazovskiy *et al.*[1] will likely generate substantial discussion in both the sleep and plasticity fields. Given the cellular and functional complexity of the brain regions sampled (whole cortex, whole hippocampus), it is amazing that there are any unified biochemical or functional changes with this level of analysis. The simplest interpretation of the data, that synaptic strength is changing, is a reasonable working hypothesis. Molecules induced by sleep deprivation suggest that prolonged wakefulness itself might cause changes in neuronal signal transduction coupling that could influence synaptic strength[9]. Moreover, the diversity of cell

types in cortex and hippocampus make it likely that other processes, such as alterations in excitability or neuromodulation, might underlie or complement the documented changes during sleep and wake. Another important question is whether the reported potentiation and depotentiation is really a scaling process. That is, are the relative strengths of all synapses maintained? Alternatively, the net change may be a summation of uncorrelated local potentiation and depotentiation events. In sum, the idea that sleep modulates synaptic strength is attractive, but studies at the synapse level are now necessary.

A number of testable predictions follow from this study that do not require synapse-level studies. Small brain nuclei with marked activity differences between sleep and wake should show even bigger upregulations of GluR1 and NR2A levels, as well as bigger changes in GluR1 and CaMKII phosphorylation, consistent with potentiation. On the basis of recent work, the hypocretin system in the posterior hypothalamus would be a good place to start; these wake-promoting neurons undergo potentiation in response to prolonged wakefulness[10]. Even more interesting will be brain nuclei that are more active in sleep than in wakefulness, such as ventrolateral pre-optic neurons[11]. They should manifest the hallmarks of potentiation during sleep rather than during wake. Inhibitory circuits will also be of interest; more potent activation during wake (or sleep) should cause increased synapse numbers and strength, yet have different biochemical signatures than excitatory inputs. Even if these kinds of studies, or those conducted at the synapse level, fail to fully confirm this sleep-wake homeostatic plasticity hypothesis[1], it is now hard to imagine that it will become irrelevant to the ‘why’ of sleep.

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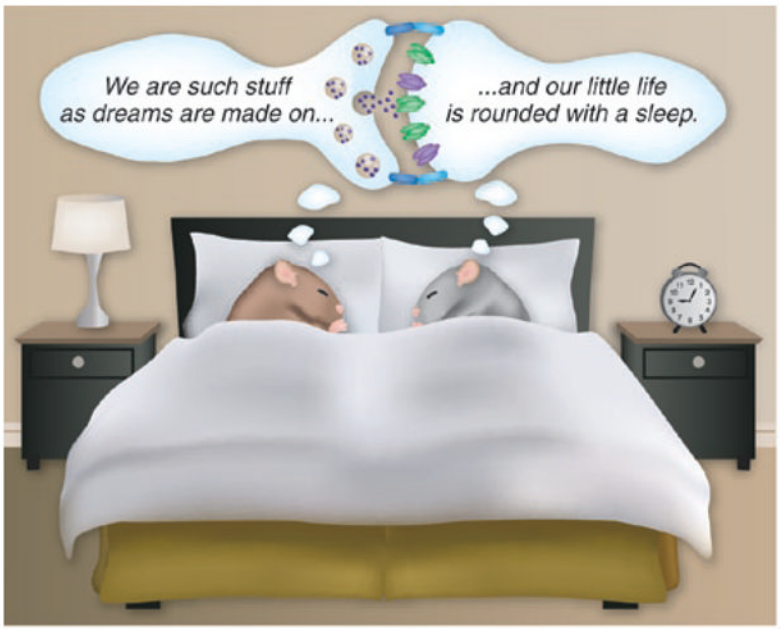

Figure 1.
The sleep state may provide an opportunity to reset synapses in the brain, depotentiating them back to baseline Awake episode is possible.