NEUROSCIENCE

Synaptic scaling in sleep

The structure of synapses changes during sleep

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Sleep appears to be a universal phenomenon in the animal kingdom (*1*) and lack of sleep leads to severe cognitive disruption (*2*). Yet, the biological function of sleep is unknown. On pages 507 and 511 of this issue, de Vivo *et al.* (*3*) and Diering *et al.* (*4*), respectively, provide a peek into the nightlife of synapses, the neural connections in the nervous system. The studies reveal substantial alterations in the structure and molecular machinery of synapses during sleep.

There are two main schools of thought for the function of sleep, which are not incompatible and may both be correct (or incorrect). "Restorative" theories hold that sleep's function is maintenance, such as repairing wear and tear in cellular machinery, replenishing energy supplies, and removing chemical waste products (*5*, *6*). "Information-processing" theories hold that sleep allows computational processes such as memory consolidation. A prominent idea is that sleep weakens synaptic connections to counterbalance the enhancement of synaptic strength that occurred during waking (*7*–*9*). De Vivo *et al.* and Diering *et al.* provide strong confirmation for synaptic downscaling during sleep and upscaling during wake as well as clues to the molecular mechanisms.

De Vivo *et al.* used block-face scanning electron microscopy on mouse brain tissue to reconstruct three-dimensional images of dendritic spines on cortical neurons in primary somatosensory and motor cortices. Spines are small protrusions on neuronal processes called dendrites, each of which is contacted by a single axon terminal that projects from another neuron. The authors found that the area of contact between an axon terminal and a dendritic spine decreases by about 20% during sleep compared to both wake and enforced wake states. However, this shrinkage of contact area on spines was only observed in the smaller 80% of the spines. Shrinking spines are more likely to contain recycling endosomes, indicating increased turnover of synaptic molecules. Because decreasing spine size probably reflects weaker synapses, the data suggest a downscaling of synaptic strength during sleep (see the figure).

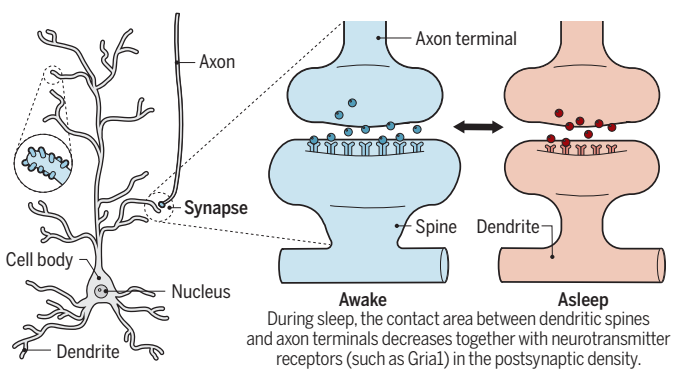
Diering *et al.* also noted a decrease in spine size and reduced presence of glutamate receptor, ionotropic AMPA 1 (Gria1) in synapses during sleep. Biochemical and proteomic analyses implicated glutamate receptor, metabotropic 5 (Grm5) and an associated scaffold protein, Homer, which links Grm5 to signaling molecules such as protein kinase C and the receptor for inositol 1,4,5-trisphosphate (IP_3). During sleep, a truncated form of Homer (Homer1a) moves to the synapse, but because it cannot fulfill the same function as the full-length protein, the IP_3 receptor signaling complex disassembles and an alternative, agonist-independent pathway leads to synaptic downscaling by decreasing Gria1 content at the synapse. Diering *et al.* implicate noradrenaline and adenosine—whose concentrations alternate with the sleep cycle—as drivers of these spine dynamics.

De Vivo *et al.* and Diering *et al.* make a good case for net synaptic weakening during sleep and strengthening during wake, yet questions still remain. What computational function might downscaling during sleep play? If sleep reduces all synapses uniformly, then presumably evolution could have found a way for this to happen during waking without requiring a long period of behavioral inactivity. Some insights may come from studies of artificial neural networks (*10*, *11*). Recurrent neural networks with Hebbian plasticity rules are inherently unstable—that is, if synchronous neural firing leads to synaptic strengthening, and strengthened synapses lead to increased synchrony, then synapses would strengthen without limit. Thus, Hebbian plasticity could be balanced against an opposing process in which synchronous activity patterns that the network generates when deprived of external input lead to synaptic weakening. Learning rules based on this principle can be shown mathematically to perform optimal Bayesian inference, and such free-running cortical activity was suggested as the basis of dreams (*10*, *11*). A related theory holds that "smart forgetting" of synapses not recently used during waking might occur during slow-wave sleep (*7*).

De Vivo *et al.* and Diering *et al.* each suggest a different scenario regarding which synapses change strength during sleep. Whereas de Vivo *et al.* report no substantial decrease in spine size for the largest (presumably strongest) synapses, Diering *et al.* report the largest decreases for spines that have the largest Gria1 content (presumably the strongest synapses). Given that only a small fraction of synapses may be involved in learning a new situation or motor skill (*12*), will they show more or less scaling in sleep? As for the precise phase of sleep in which synaptic changes occur, both rapid eye movement (REM) sleep and slow-wave sleep have been proposed as the phase when synaptic downscaling occurs (*13*). Also, the key assumption of sleep renormalization (*10, 11*)—that plasticity during sleep is reversed to become anti-Hebbian—remains unproven. Thus, although the evidence for diurnal change in synaptic strength grows, the precise computational function that this serves remains as mysterious as ever. ■

Spine dynamics

Synaptic connections are altered between sleep and wake states.



During sleep, the contact area between dendritic spines and axon terminals decreases together with neurotransmitter receptors (such as Gria1) in the postsynaptic density.

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