NEUROSCIENCE

Sleep It Out

Change in the brain's extracellular space between sleep and waking states may drive the clearance of metabolites and toxins.

Suzana Herculano-Houzel

We know from personal experience that sleep is not just another brain state but a basic requirement for normal brain function while we are awake. Mental fatigue, poor decision-making, impaired learning, and a heightened risk of migraine and epileptic attacks ensue when we are sleep deprived—and chronic and complete insomnia ultimately lead to death in humans, rats, and flies alike (*1*). Why does normal brain function deteriorate with prolonged waking and require sleep to be restored? On page 373 in this issue, Xie *et al*. (*2*) report that during sleep, waste products of brain metabolism are removed from the interstitial space among brain cells where they accumulate. Sleep, therefore, might be required for potentially toxic metabolites—the very results of a working brain—to be cleared from the tissue.

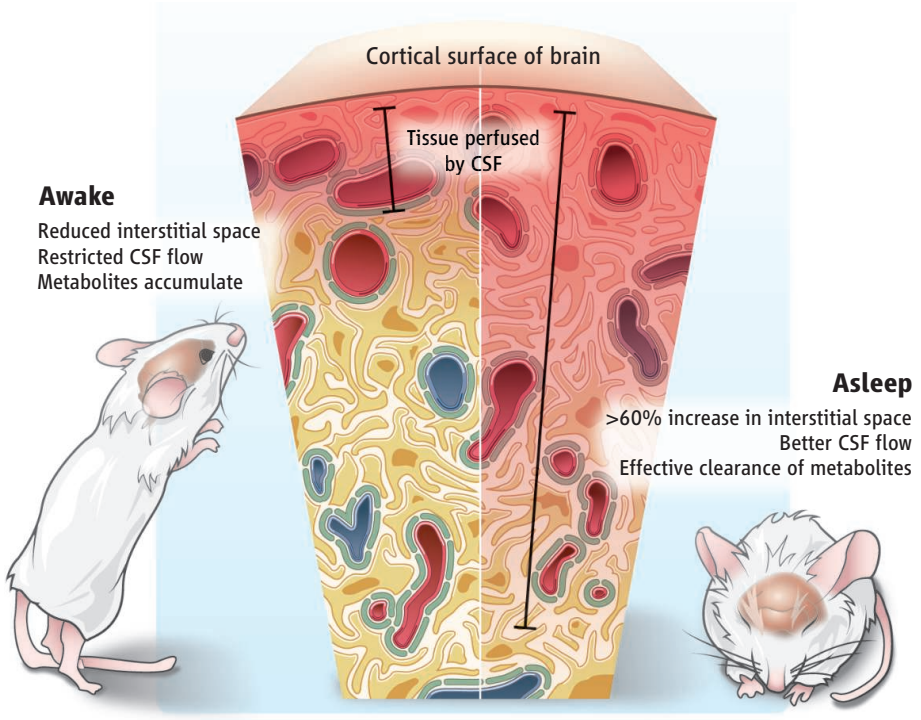
The interstitial space between cells in a tissue is an underappreciated component of the nervous system, considering that it amounts to ~20% of the total volume of the living, anesthetized brain (*3*)—which is the state in which most studies of brain physiology are made. In the absence of a lymphatic system in the brain, the interstitial space performs its duties, removing waste products that brain cells secrete. These metabolites are flushed away through the interstitial space by the flow of cerebrospinal fluid (CSF), which is filtered from blood and pumped into the brain by the choroid plexus at the ventricles, seeps through the interstitial space among brain cells, and is eventually pumped back into the blood stream at the meninges that surround the brain.

By applying real-time iontophoresis (to observe fluid flow), Xie *et al*. estimate that the interstitial space in the waking mouse brain is only 14% of brain volume, but increases by over 60% in natural sleep or anesthesia to 23% of the brain volume (see the figure). This might appear to be a relatively modest increase in interstitial space, but has remarkable consequences for the flow of CSF and the substances carried in it. Using fluorescent tracers injected into the CSF and visualized by two-photon microscopy of the exposed mouse brain, the authors find that in waking, CSF flow is restricted to the brain surface—but expands deep into the tissue during both natural sleep and anesthesia. The consequence is remarkable: The flow of CSF through the interstitial space is reduced during waking to only 5% of the flow found in sleep. Moreover, both the constriction of interstitial space and the restriction of CSF flow through it observed in natural waking can be mimicked by the application of a noradrenergic agonist to the surface of the sleeping brain. This molecule simulates the release of noradrenaline, which only occurs in the brain during waking. Noradrenaline modulates neuronal activity, which can alter the volume of the interstitial space (*4*) by causing cells to swell in the presence of the elevated extracellular K^+ concentration that results from neuronal activity (*3*). The state-dependent constriction of this space might thus be a direct consequence of the molecules associated with waking.

The striking increase in CSF flow through the interstitial space during sleep results in much more efficient clearance from the brain of metabolites, such as β-amyloid (Aβ), a peptide that accumulates during waking and that has been implicated in the progression of Alzheimer's disease. Xie *et al*. found that both radiolabeled Aβ and another inert tracer injected into the cerebral cortex are cleared two times as fast from the brain in sleeping compared to waking mice.

Xie *et al*. propose that the restorative function of sleep may be due to switching of the brain into a state that facilitates the clearance of degradation products of neural activity that accumulate during wakefulness. But going one step further, it is possible that the very accumulation of metabolites during waking, forced by the constricted interstitial space, drives the switch to sleep state. This then allows the clearance of metabolites and prepares the brain for a new bout of waking, in an obligatory, self-regulating, and never-ending alternation of brain states.

A similar idea was behind the proposition that adenosine, a metabolite of both neuronal and glial activity, serves as a sleep-induc-



Volume variation. The extracellular (interstitial) space in the cortex of the mouse brain, through which cerebral spinal fluid moves, increases from 14% in the awake animal to 23% in the sleeping animal, an increase that allows the faster clearance of metabolic waste products and toxins. Therapeutics could potentially exploit this dynamic to clear factors associated with conditions such as epilepsy, migraines, and insomnia.

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ing molecule that underlies the homeostatic drive for sleep (*5*). The concentration of adenosine in the brain increases during waking, accumulates even more with sleep deprivation, and decreases rapidly during sleep (*6*), even during only brief intrusions of sleep into forcefully prolonged wakefulness (*7*). The findings by Xie *et al*. offer a testable explanation for this fast restorative effect of intrusive sleep—the dissipation of sleep pressure as metabolites, such as adenosine, are rapidly swept away.

The observations of Xie *et al*. should spark interest in the state-dependent clearance of waste metabolites, as the wake-shrinking interstitial space presents a good place to look for factors whose accumulation during waking heightens sensitivity to migraines and epileptic seizures, and worsens other conditions associated with insomnia. The development of drugs that facilitate clearance of waste products during waking is also a new possibility.

The newfound interest in the interstitial space of the brain and how it relates not only to metabolite clearance but also to brain states might also help resolve another sleep-related conundrum: the relationship between the number of hours of sleep characteristic of each species and their brain size (*8*). Sleep is universal among vertebrates (*9*) and has been found in invertebrates (*9*, *10*). The total number of hours of daily sleep varies from as much as 20 hours in bats to as little as 3 to 4 hours in giraffes and elephants (*8*, *11*)—and there is currently no reasonable physiological hypothesis to explain this variation (*11*). Because CSF perfusion of the interstitial space is limited to the surface of the brain during waking, and brain volume increases faster than brain surface area [even with the folding of the cortical surface (*12*)], larger brains should have a relatively larger volume of interstitial space to "buffer" the accumulation of sleep-driving molecules, and thus might be able to withstand much longer periods of waking before the inevitable switch to the waste-clearing state of sleep occurs. If only neuroscientists could easily bring live, large-brained animals to the lab.

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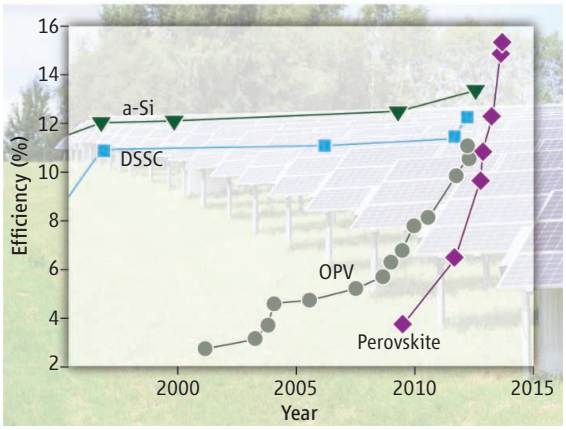
APPLIED PHYSICS

Perovskite-Based Solar Cells

Organic-inorganic hybrid semiconductors may provide the basis for the next generation of thin-film solar cells.

Gary Hodes

Photovoltaic (PV) cells that convert sunlight directly into electricity are becoming increasingly important in the world's renewable energy mix. The cumulative world PV installations reached around 100 GW_p (gigawatts) (*1*) by the end of 2012. Some 85% use crystalline Si, with the rest being polycrystalline thin film cells, mostly cadmium telluride/cadmium sulfide ones. Thin-film cells tend to be cheaper to make with a shorter energy payback time. However, they do have the disadvantage, one that may become crucial when considering the terawatt range, that most of them contain rare elements like tellurium (as rare as gold), indium, and gallium. A newcomer to the PV field (*2*) has rapidly reached conversion efficiencies of more than 15% (see the figure). Based on organic-inorganic perovskite-structured semiconductors, the most common of which is the triiodide ($CH_3NH_3PbI_3$), these perovskites tend to have high charge-carrier mobilities (*3*, *4*). High mobility is important because, together with high charge carrier lifetimes, it means that the light-generated electrons and holes can move large enough distances to be extracted as current, instead of losing their energy as heat within the cell. On pages 344 and 341 of this issue, Xing *et al*. (*5*) and Stranks *et al*. (*6*) use time-resolved transient absorption and photoluminescence to show that the effective diffusion lengths are indeed relatively large in $CH_3NH_3PbI_3$, about 100 nm for both electrons and holes—a high value for a semiconductor formed from solution at low temperature.



Onward and upward. Comparing the rate of increase in perovskite solar cell efficiencies (purple lines and markers) with leading third-generation (i.e., relatively new) solar cells and with amorphous Si (a-Si), green; dye sensitized, blue; organic, gray. The first two perovskite cells (2009 and 2011) refer to liquid junction cells, which were not stable but were important in initiating the subsequent solid-state cells. The last three cell types are taken from www.nrel.gov/ncpv/images/efficiency_chart.jpg.

Another important consideration for these perovskites is that they are deposited by low-temperature solution methods (typically spin-coating). The low energy and ease of deposition is of obvious importance for eventual manufacturing of the cells. It also greatly emphasizes the importance of the diffusion lengths described in these two papers for $CH_3NH_3PbI_3$. For those working on more conventional semiconductor films, the reported diffusion lengths of 100 nm may not appear to be special. However, low-temperature (below 100°C) solution-processed films tend to have considerably smaller diffusion lengths. Stranks *et al*. had previously described nanostructured cells using $CH_3NH_3Pb(I,Cl)_3$ (essentially the iodide with a small amount of chloride) (*7*) and demonstrated a thin-film solar cell (not nanostructured) with an

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