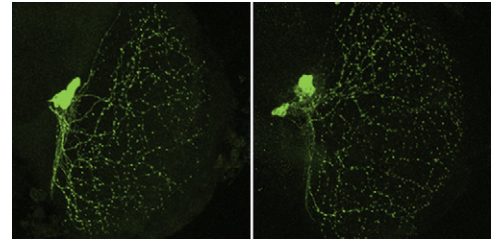


Sleep is one of the most fundamental, yet least understood, facets of animal physiology—its universality reflected in the saying, “life is one long process of getting tired.” This issue’s Neurobiology Select describes the latest progress toward understanding sleep, including its role in maintaining synaptic homeostasis, its role in long-term memory formation, and the causes and consequences of sleep disruption.

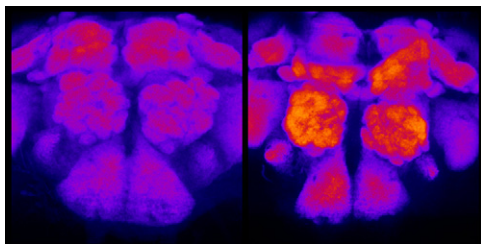
## After a Party, Flies Sleep It Off

If attending a party full of strangers leaves you exhausted, you may have something in common with the fruit fly *Drosophila*. In their latest work, Donlea et al. (2009) have uncovered a neural basis for the increased need for sleep that fruit flies display after social enrichment. The authors first identify mutant flies that do not have an increased need for sleep after social enrichment, in this case housing flies in groups rather than in isolation. These mutant flies include those lacking the *rutabaga* gene (involved in memory formation), *period* (a core regulator of the circadian cycle), and *blistered* (implicated in long-term potentiation at synapses). The authors then sought to define which population of neurons requires *rutabaga*, *period*, and *blistered* for this behavior and show that reestablishing expression of these genes in ventral lateral neurons restores the increased need for sleep after social enrichment. Ventral lateral neurons are a group of clock neurons that control circadian behavior in flies. Close examination reveals that social enrichment enhances the number of synapses between ventral lateral neurons and neurons of the medulla. Remarkably, sleep reduced the number of these synaptic connections, and this reduction is blocked by sleep deprivation. These findings suggest that this synaptic plasticity in ventral lateral neurons underlies the need for sleep, and provides a compelling example of sleep being required for synaptic homeostasis.

J.M. Donlea et al. (2009). *Science* **324**, 105–108.



Ventral lateral neuron projections in socially enriched flies (right) contain more green fluorescent protein-positive synaptic terminals than their socially isolated siblings (left). Image courtesy of P. Shaw.



Expression of Bruchpilot, an indicator of synapse number, is heightened in the nervous system of sleep-deprived fruit flies (right) compared to controls (left). Image courtesy of C. Cirelli.

## Synapses Kick Back at the End of the Day

A different means by which sleep maintains synaptic homeostasis is reported by Gilestro et al. (2009), who examined the expression of synaptic proteins in *Drosophila* at intervals throughout the day to analyze the potential impact of sleep on synaptic function. They observe a consistent pattern—the levels of synaptic proteins are lowest after sleep. This finding suggests that individual synapses build up protein levels during the day as a consequence of neuronal activity, and clean house at night in preparation for the following day. This reduction in synaptic protein levels is not simply a feature of the circadian cycle, given that sleep deprivation blocks the reduction. This work raises many interesting questions, including whether the reduction in synaptic proteins during the night is a general feature of the nervous systems of other species. In prior work, this group has observed in sleeping rats a similar decline in the expression of AMPA

receptors containing the GluR1 subunit. Future efforts may also examine the mechanisms linking sleep to synaptic protein degradation and determine whether disruption to sleep-dependent protein degradation has effects on learning and memory. G.F. Gilestro et al. (2009). *Science* **324**, 109–112.

## A Neural Network Goes Bump in the Night

Long-term memories are believed to be gradually established across distributed cortical networks under the influence of the hippocampus. However, it remains unclear how memories are transferred between the two brain regions, a process termed memory consolidation, although sleep is thought to be involved in this process. Wierzynski et al. (2009) now describe a circuit between the hippocampus and prefrontal cortex that may aid in memory consolidation. The authors analyze neural spikes of naturally sleeping rats and discover a consistent relationship between the activity of hippocampal and prefrontal circuits, in which firing of CA1 hippocampal neurons is followed within 100 ms by firing of neurons in the prefrontal cortex. This unidirectional flow of information is consistent with a mechanism for memory transfer between the two brain regions. Interestingly, the spike-timing relationship occurs during slow-wave sleep, the sleep phase thought to be critical for memory consolidation. Do

these timed bursts of activity transmit quanta of information about memories? If so, a topic for future work will be to establish how these units of information are then coded in the prefrontal cortex for long-term storage.

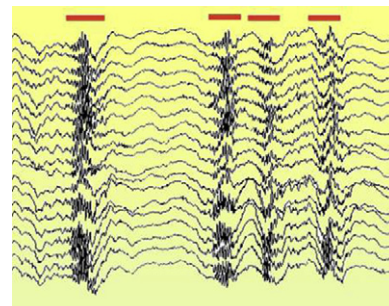
C.M. Wierzynski et al. (2009). *Neuron* **61**, 587–596.

## Giving Orexin Neurons a Wake Up Call

Thyrotropin-releasing hormone (TRH) promotes wakefulness, but the neural circuitry underlying this effect has been unclear. Hara et al. (2009) now provide evidence that the TRH produced by neurons of the dorsomedial hypothalamic nucleus promote wakefulness by acting on the hypocretin/orexin-producing neurons in the lateral hypothalamic area. The orexins are neuropeptide hormones that are well-known regulators of arousal and energy homeostasis. The authors show that the effects of TRH on orexin neurons are multifaceted—TRH directly engages receptors on orexin neurons to increase their firing rate and indirectly modulates orexin neurons by decreasing their excitatory glutamatergic input and increasing their inhibitory GABAergic input. The effects of altering GABAergic input to orexin neurons are examined in related work by Matsuki et al. (2009). These authors establish a spatially restricted knockout mouse that lacks expression of a key subunit of the metabotropic GABA<sub>B</sub> receptor in orexin neurons, which results in reduced responsiveness of orexin neurons to both excitatory and inhibitory inputs. The impact on sleep/wake cycles is equally pronounced. Although the transgenic mice slept a similar amount of time compared with control mice in a 24 hour period, the duration of individual episodes of wakefulness, REM sleep (sleep characterized by rapid eye movements), and non-REM sleep were markedly shorter. Future work may explore the authors' proposal that the sleep fragmentation found in these mice could offer clues to disrupted sleep patterns in the elderly.

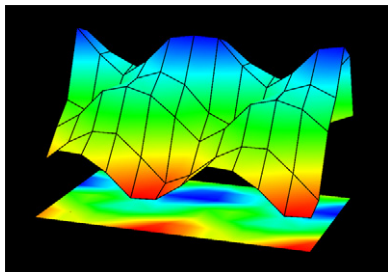
J. Hara et al. (2009). *J. Neurosci.* **29**, 3705–3714.

T. Matsuki et al. (2009). *Proc. Natl. Acad. Sci. USA* **106**, 4459–4464.



Local field potentials from area CA1 in the hippocampus during slow-wave sleep. Ripple bursts (red lines) drive coordinated spiking activity in the prefrontal cortex. Image courtesy of T. Siapas.

## Hazards of the Night Shift



Changes in plasma leptin levels from circadian and behavioral cycle misalignment. Image courtesy of F. Scheer.

Although the normal pattern of sleep/wake cycles may be set by the brain, disrupting this schedule has effects throughout the body. Scheer et al. (2009) compile a disconcerting list of metabolic, hormonal, and cardiovascular changes that occur when the regular cycles of eating and sleeping are knocked out of synch with the body's circadian clock. To simulate jet lag or the experience of shift workers, Scheer et al. placed ten human subjects on a schedule with a 28 hr day. They then analyzed their metabolic and cardiovascular functions over eight of these lengthened days as the subjects' behavioral cycle (eating and being awake) became progressively misaligned with their internal circadian clock. This allowed the authors to independently analyze the effects of the behavioral cycle and the circadian cycle. The effects of the misalignment are striking. When the behavioral cycle is offset by 12 hours from the normal circadian cycle (such that the subjects are awake and eating when they normally would be sleeping), the subjects displayed increased arterial blood pressure, decreased circulating leptin, and had higher levels of blood glucose, despite an

increase in insulin. The elevation in glucose after eating was sufficiently pronounced that some subjects would have been classified as prediabetic were these measurements obtained in a routine visit to a doctor's office. These findings are consistent with epidemiological studies indicating that routinely working the night shift increases the risk of obesity, diabetes, and cardiovascular disease and reveal potential underlying mechanisms. By identifying facets of human physiology most affected by a shift in sleep schedule, the authors hope to reveal new ways of mitigating the worst effects of circadian misalignment. Future work may explore whether light or melatonin treatment, for instance, alleviate a subset of these adverse symptoms.

F.A.J.L. Scheer et al. (2009). *Proc. Natl. Acad. Sci. USA* **106**, 4453–4458.

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