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## Researchers Find the Snooze Button

With help from some drowsy fruit flies, a team of researchers from the Howard Hughes Medical Institute (HHMI) at the University of Pennsylvania School of Medicine has identified a region of the fruit fly's brain that is crucial to controlling sleep.

The finding, reported in the June 8, 2006, issue of the journal *Nature*, is important because it identifies a new role for brain structures, called mushroom bodies, which have now been shown to control fruit fly slumber. Mushroom bodies were known to be involved in processing sensory information and memory. Thus, the new studies lend support to the idea that sleep helps the brain consolidate learning and memory.

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We spend one-third of our lives sleeping, but we know very little about sleep and how it is regulated, explained Amita Sehgal, the senior author of the new *Nature* paper and an HHMI investigator at the University of Pennsylvania School of Medicine. It's really pretty amazing that we know so little.

Sleep, in fact, is such a mystery that scientists are not even sure why animals require it. No purpose or underlying mechanism for the phenomenon has ever been proven.

And while the new *Nature* report does not delve directly into the mysteries of why animals snooze, the findings support the idea that one of sleep's essential roles is to limit sensory input so the brain can organize and crystallize the day's memories for storage and future retrieval.

The research actually doesn't tell us much directly about the purpose of sleep, said Sehgal. But one of the things suggested (from past research) is that sleep helps consolidate memory.

Consequently, the finding by Sehgal and her colleagues showing that sleep and memory share a common locus in the brain may begin to substantiate why our brains must routinely descend into the idling metabolic and electrical

state that defines sleep.

Sehgal's group conducted a series of experiments with sleeping flies that fingered mushroom bodies as at least one of the brain's primary snooze buttons.

Mushroom bodies are an anatomical structure in the fly brain, mostly associated with learning and memory, said Sehgal, who conducted the research at Penn's Center for Sleep and Respiratory Neurobiology. They also process olfactory cues and locomotor activity.

In insects, mushroom bodies are already known to be involved in learning and memory functions, especially those associated with the chemical odors that underpin much of the communication that transpires in the insect world.

It is possible, Sehgal and her colleagues speculate, that the mushroom bodies constitute a gate to fly dreamland: sleep occurs when the stream of sensory information processed by the structure — an elaborate net of neural cells — is inhibited.

In humans and other higher animals, sleep has been associated with several different structures in the brain, mostly by looking at brain waves, the patterns of electrical signals generated during sleep or wakefulness. There are no structures analogous to mushroom bodies in vertebrates, but the hippocampus and/or thalamus may harbor a similar control center for human sleep, Sehgal noted.

One of the things that makes it difficult to study sleep is that it doesn't map to one particular locus in the brain, she said. In the fly, the mushroom bodies are probably not the only thing associated with sleep.

However, the new HHMI study opens the door to a deeper understanding of the phenomenon of snoozing by identifying an anatomical feature that regulates it. Knowing that sleep is controlled by the mushroom bodies means that it is now possible to begin to ferret out the molecular processes that determine if we are sleepy or alert, said Sehgal.

Once you have (linked sleep to an anatomical structure), you can figure out changes taking place at the molecular level in that region of the brain, Sehgal explained. It allows us to shift our efforts to see what happens during sleep and what happens when we're awake that leads to sleep.

The HHMI team was able to home in on mushroom bodies' role in regulating sleep in flies by using the drug RU-486 in their studies. The drug is a synthetic steroid that researchers can use as a way to control the expression of genes in specific brain regions.

RU-486 is a steroid that acts on steroid-regulated promoters, she explained. We used RU-484-responsive sequences to control our gene of interest and once we had done that in the fly, we could feed the fly RU-486 to turn that gene on.

Sehgal and her team were then able to induce large changes in sleep by using RU-486 to manipulate a critical gene known as protein kinase (PKA), which makes a protein that, in the brain, activates other proteins and switches other genes on or off.

In flies, the duration of sleep is inversely related to PKA activity. By expressing the gene in different regions of the brain, including mushroom bodies, it was possible to assess the roles of those structures in the phenomenon of sleep.

Sehgal said that a fly is sleeping if it remains motionless for extended periods. At the moment, our definition of fly sleep is five minutes of immobility, she explained. A camera and computer programmed to detect fly motion were used to confirm the state.

In addition to identifying the structure that governs sleep in invertebrates, the new HHMI work promises to help researchers zero in on the anatomical structures in the brains of higher animals, including humans, which govern sleep.

Co-authors of the new *Nature* study include William J. Joiner and Amanda Crocker of the University of Pennsylvania's Center for Sleep and Respiratory Neurobiology, and Benjamin H. White of the National Institute of Mental Health in Bethesda, Md.