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RESEARCH NEWS

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Fruit Fly Study Yields a Gene Required for Peaceful Slumber

After a sleepless night, anyone - even a fruit fly - can feel a little groggy, and a lot of mystery surrounds what keeps us up at night. Now, thanks to a set of fruit flies that seem to get by with far less dozing than most, a team of Howard Hughes Medical Institute (HHMI) researchers has found a gene absolutely necessary for snoozing.

The discovery of the slumber gene, dubbed SLEEPLESS, is reported in the July 18, 2008 issue of the journal *Science*. The finding, which was made by a group led by HHMI investigator Amita Sehgal and her colleagues at the University of Pennsylvania School of Medicine, could one day help scientists puzzle out some of the root causes of chronic sleep problems.

“Sleep serves an essential function, although we don't know what that is,” explained Sehgal. The discovery of SLEEPLESS “allows us to start to get a handle on the mechanisms underlying sleep.”

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> **- Amita Sehgal**

Sleep is a universal requirement, occurring in animals from flies to humans. It is controlled by the body's circadian clock -- a roughly 24-hour cycle in the biochemical, physiological and behavioral processes of animals -- as well as by an organism's internal equilibrium. A fruit fly can sleep up to 12 hours a day.

Without sleep, animals will die. The SLEEPLESS mutants in Sehgal's study live only half as long as a typical fly. “Even the SLEEPLESS animals need sleep -- that's probably why they are so short lived,” she said.

Sehgal and her colleagues homed in on SLEEPLESS by sorting through more than 3,500 mutant fruit fly lines, selecting the line of flies that slept the least each day. That line, according to Sehgal, survives on a sleep regimen that is

at least 80 percent less than that of an ordinary fruit fly. About nine percent of those flies appear to even get by without sleeping a wink -- all attributable to the mutation of a single gene.

“SLEEPLESS affects the duration as well as the number of sleep bouts” a fly experiences, said Sehgal. “We think it is required to initiate a sleep state.”

Fruit flies sleep differently than humans. They do not close their eyes, and as far as scientists know they don't go through the different stages of sleep typical of mammals. At rest, however, they resemble sleeping humans in many ways. For example, they sleep at night, they do not respond to stimuli, they try to make up for lost sleep, and they get groggy when deprived of shut-eye.

The researchers found that the SLEEPLESS gene encodes a protein that, when tamped down in mutant flies, seems to prompt a remarkable reduction in both the number and duration of sleep episodes. Sehgal's group found that flies without the SLEEPLESS protein experience an extreme loss of sleep. Flies in which the level of SLEEPLESS is merely reduced experience normal baseline sleep. However, when those flies are sleep deprived, the duration of their “recovery sleep” is compromised.

“The protein is small, as proteins go,” she said, “and most likely affects signaling.”

The thought, she said, is that the protein influences sleep by regulating potassium ion channels, pores in cell membranes that regulate the flow of ions into and out of cells. It suggests that control of membrane excitability is a critical requirement for sleep.

“You have to silence at least some groups of neurons for sleep to occur,” according to Sehgal. “Neurons that promote arousal have to be silenced and one way to do that is through potassium channels.”

The discovery of SLEEPLESS is surely only part of the story of the biology of sleep, Sehgal emphasized. There are certainly more genes at work, but having a key gene in hand will help scientists tease out more of the molecular secrets of slumber.

“Now we can figure out where in the fly brain SLEEPLESS is required,” she noted, “and we can start looking at SLEEPLESS animals to see what's going on biochemically.”

Those explorations may yield clues about the very nature of sleep and why it is so important. Although Sehgal and her group have not identified a similar gene in humans, she says it is very likely that one exists and could provide more insight into human slumber and sleep disorders.