Starvation keeps sleep-deprived fly brain sharp

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As anyone who has ever struggled to keep his or her eyes open after a big meal knows, eating can induce sleepiness. New research in fruit flies suggests that, conversely, being hungry may provide a way to stay awake without feeling groggy or mentally challenged.

Scientists at Washington University in St. Louis found that starvation allows the need for nourishment to push aside the need for sleep. Like humans and rats, fruit flies cannot survive without sleep. But in a line of flies engineered to be sensitive to sleep deprivation, starvation nearly tripled the amount of time they could survive without sleep.

Researchers showed that the ability to resist the effects of sleep loss was linked to a protein that helps the fruit fly brain manage its storage and use of lipids, a class of molecules that includes fats such as cholesterol and fat-soluble vitamins such as vitamins A and D.

"The major drugs we have to either put people to sleep or keep them awake are all targeted to a small number of pathways in the brain, all of them having to do with neurotransmission," says Paul Shaw, PhD, assistant professor of neurobiology and anatomy. "Modifying lipid processing with drugs may provide us with a new way of tackling sleep problems that is more effective or has fewer side effects."

The study appears online Aug. 31 in *PLoS Biology*.

The findings add a new wrinkle to the complex relationship between

sleep and dietary metabolism. Scientists recognized about a decade ago that inadequate sleep results in obesity and contributes to the development of diabetes and coronary disease. Until now, no one had connected genes linked to lipids with regulation of the need for sleep.

Clay Semenkovich, MD, a Washington University lipid expert not directly involved in the study, says the results fit into a growing awareness that organisms use lipids for much more than energy storage.

"It's becoming apparent that fats serve as signaling molecules in a number of contexts," says Semenkovich, the Herbert S. Gasser Professor of Medicine. "If you identify the appropriate lipids involved in sleep regulation and figure out how to control them, you may be able to decrease suffering associated with loss of sleep or the need to stay awake."

Shaw uses fruit flies as models for sleep's effects in higher organisms. He was among the first to prove that flies enter a state comparable to sleep, showing that they have periods of inactivity where greater stimulation is required to rouse them. Like humans, flies deprived of sleep one day will try to make up for it by sleeping more the next day, a phenomenon referred to as sleep debt. Sleep-deprived flies also perform poorly on a simple test of learning ability.

Studies in other labs have shown that starvation or, in the case of human volunteers, fasting leads to less sleep. More recent research has also shown that starvation can change the activity levels of genes that manage storage and use of lipids.

Shaw's lab previously demonstrated that fruit flies with a mutation in a timekeeping gene accumulate sleep debt much more quickly and begin dying after being kept awake for as little as 10 hours. Matt Thimgan, PhD, a postdoctoral research associate, reports in the new paper that

starving fruit flies spent more time awake, and starving fruit flies with the timekeeping gene mutation could survive up to 28 hours without sleep.

Scientists tested the starving, sleepless flies for two markers of sleep debt: an enzyme in saliva and the flies' ability to learn to associate a light with an unpleasant stimulus. Both tests showed that the starving flies were not getting sleepy.

"From an evolutionary perspective, this makes sense," Thimgan says. "If you're starving, you want to make sure you're on the top of your game cognitively, to improve your chances of finding food rather than becoming food for someone else."

Scientists found an effect similar to starvation in fruit flies where a gene called Lipid storage droplet 2 (LSD2) was disabled. After sleep deprivation, flies with the LSD2 mutation were less likely to sleep for longer periods of time and continued to score high on the learning test.

"LSD2 mutants seem to constantly rotate lipids through their storage depot in cells, putting them in and moving them out very quickly," Thimgan says. "Disabling LSD2 appears to make it hard for cells to hold on to lipids and use them properly, and we think this impairs brain cells' ability to respond to sleep deprivation."

Researchers are working to identify the specific lipids affected by loss of LSD2.

More information: Thimgan MS, Suzuki Y, Seugnet L, Gottschalk L, Shaw PJ. The Perilipin homologue, Lipid storage droplet 2, regulates sleep homeostasis and prevents learning impairments following sleep loss. PLoS Biology, Aug. 31, 2010. doi:10.1371/journal.pbio.1000466
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