Researchers identify sleep gene

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Zeroing in on the core cellular mechanisms of sleep, researchers at University of Wisconsin Medical School have identified for the first time a single gene mutation that has a powerful effect on the amount of time fruit flies sleep.

In its normal state, the Drosophila (fruit fly) gene, called Shaker, produces an ion channel that controls the flow of potassium into cells, a process that critically affects, among other things, electrical activity in neurons. A handful of recent studies suggest that potassium channels are also involved in the generation of sleep in humans.

Reported in the April 28 issue of Nature, the finding points to novel approaches to treating sleep irregularities in humans-from promoting restorative sleep to prolonging wakefulness.

"This research offers the possibility of developing a new class of compounds that could affect potassium channels in the brain rather than other brain chemical systems targeted currently," says lead author Dr. Chiara Cirelli, assistant professor of psychiatry at UW Medical School.

UW-Madison genetics professor Barry Ganetsky, likely the world expert on the Shaker gene, was a collaborator on the study. Dr. Giulio Tononi, UW Medical School professor of psychiatry, was the senior author on the paper.

Most people sleep seven to eight hours a night, and if they are deprived of sleep, their cognitive performance suffers greatly. However, a few people do well with just three or four hours of sleep-a trait that seems to run in families.

"We wanted to determine which genes underlie this phenomenon in order to shed light on the mechanisms and functions of sleep," Tononi says.

The Wisconsin study focuses on factors that control sleep duration as opposed to the timing of when sleep occurs, which is regulated by the circadian system, Tononi notes. "The key molecular mechanisms controlling the circadian timing of sleep are well understood, but details about the homeostatic mechanism that regulates the amount of sleep have been unclear," he says.

In a four-year, round-the-clock search, researchers screened 9,000 mutated fruit flies, many of them supplied by Ganetsky's lab, and found one line of them that slept one-third the amount of normal flies. Put through a series of tests, the short-sleeping flies, named minisleep (mns), were found to perform normally and did not appear to be impaired by sleep deprivation. The mns flies, however, did have shorter life spans.

Following the testing, the researchers noticed shaking in the flies' legs as the insects recovered from anesthesia. The observation led the team to focus on the Shaker gene, which produces this effect. Nevertheless, Shaker's main job in flies-and in its equivalent in humans-is to control the excitability of cell membranes.

Genetic analysis of the mns flies, conducted by Daniel Bushey, a post-doctoral fellow working with the Tononi team, revealed that their Shaker genes contained a single amino-acid mutation. Because of the mutation, a functional ion channel could not be formed on the cell membrane and potassium therefore could not flow through it.

When the researchers first tested flies with the Shaker gene, they found that some of them with other mutations were normal sleepers. But these flies became short sleepers when the researchers removed genetic modifiers from their genome.

"This told us that genetic forces push hard against this phenotype to make it ineffective," Cirelli says. "Being a short sleeper is probably not a good thing. We know that the mns mutation affects mortality, but we're not sure how."

In earlier studies, Tononi's team discovered that fruit flies do, in fact, sleep.

"The more behaviors we look at, in terms of sleep, the more we find that sleep in fruit flies is very, very similar to sleep in mammals," Cirelli says.

Like humans, fruit flies generally are quiet and immobile for between six and 12 hours each night and lose most of their ability to respond to stimuli, the researchers found. When deprived of sleep, humans and their winged counterparts rebound on the following night by sleeping longer and more deeply. Flies also sleep more in their youth than later in life, when their sleep is fragmented, as with humans.

In other studies, the scientists also observed that caffeine has the same stimulating effects on human and fly sleep, and that similar genes are expressed in both species when they are awake and asleep. Tononi's team also conducted EEGs on the flies and found evidence of the same electrophysiological changes occurring during sleep and wakefulness as in humans.

"The electrical changes in humans look different that they do in flies because our brains are organized differently," Cirelli says. "But the

EEGs showed electrophysiological changes signifying that the flies were asleep and awake."

In mammals the changes produce hallmark waves, or oscillations of groups of neurons, easily detected by EEG. The waves are slower during deep sleep and faster during waking times. One way of getting from the faster to the slower state is by opening ion channels, allowing potassium to flow through them.

"Our hypothesis is that if you don't have potassium channels, you won't get slow waves," Cirelli says. "The cell membrane will remain activated, preventing long periods of deep, non-REM sleep."

The researchers say that the fly research translates to humans even more than they thought it would. "Humans have the same kind of genes and potassium channels. And we know that slow waves must be generated by changes in the excitability of neuron cell membranes," Cirelli says. "Potassium changes may have a huge affect on sleep in humans."

Sleep is a highly complex activity and probably involves many genes, some of which are more influential than others, says Cirelli. "We believe this gene is very powerful because it acts on the final common pathway and has the ability to change the excitability of neurons."

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