NEWS

Fragile X protein may control sleep span, study suggests

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Sustained slumber: Fruit flies lacking the fragile X gene sleep longer than do normal flies and develop overgrown neurons.

The genetic culprit in fragile X syndrome — a form of mental retardation frequently accompanied by autism — can alter how much fruit flies sleep, according to a study published in the *Journal of Neuroscience* [1].Flies that lack FMR1, the gene missing in people with fragile X, sleep longer than do normal flies. Flies (and humans) usually sleep longer and more intensely after a period of sleep deprivation, but flies that are missing FMR1 don't show this ‘sleep rebound’.

These findings, published in February, may help explain the sleep difficulties of some patients with fragile X, up to 30 percent of whom also have autism[2].

The study expands the role of FMR1 in sleep, says **David Nelson**, professor of molecular and human genetics at Baylor College of Medicine in Houston, Texas. Nelson previously found a link between FMR1 and circadian rhythms — the physiological processes that govern when an organism sleeps — in mice and flies[3,4].

FMR1 codes for the fragile X mental retardation protein, or FMRP. Fragile X syndrome occurs in people who don't make functional FMRP. The new study is the first to link FMRP to the amount of time an organism spends sleeping, or ‘sleep need’, rather than to when it sleeps.

Comparing flies with humans is complicated, however, because FMRP’s function in flies is likely to be shared among several genes in humans, Nelson says.

The scientists who led the new study initially designed the fly experiments in order to better understand the function of normal sleep. The researchers propose that the amount of time an organism sleeps is determined by the amount of electrical activity in synapses, the junctions between neurons in the brain. Learning spurs molecular changes at the synapse, boosting the electrical signals that pass through.

“The general idea that we are testing is that the more you use your neurons and strengthen your synapses during waking, the more you need to sleep,” says **Chiara Cirelli**, associate professor of psychiatry at the University of Wisconsin–Madison. Maintaining stronger synapses is energetically expensive, according to Cirelli. Some studies have suggested that sleep curbs this unsustainable growth by weakening strong synapses and culling weak ones[5].

To test this idea, the researchers studied both fruit flies lacking FMRP and fruit flies with excess FMRP. Flies that lack FMRP have overgrown dendrites — the branches of neurons that receive signals from other neurons — with many synapses; those with too much FMRP have scrawny dendrites with fewer synapses.

According to the researchers' hypothesis, these two types of flies should have different sleep needs: those with more synapses should need more sleep, whereas those with fewer synapses should need less.

To monitor sleep in flies, the scientists looked for periods when the flies were not moving. By measuring how often a fly crossed an infrared beam transmitted through its test-tube home, the scientists found that, on average, flies missing FMRP sleep four hours longer than do control flies in a 24-hour period. In contrast, flies with excess FMRP sleep about three hours less than do control flies.

Although this matches Cirelli’s prediction, she is cautious about what it means for her hypothesis about sleep’s function. “This is absolutely only a correlation,” she says, citing the need for an experiment that tracks whether the number of synapses changes between sleeping and waking periods in these flies.

Flies to humans:

The researchers also tested how the flies react to sleep deprivation. They first deprived flies of sleep for 24 hours by mechanically shaking their test tubes. Neither the flies lacking FMR1 nor those overexpressing FMR1 exhibited a sleep rebound: their total sleep duration went unchanged, and they didn’t sleep any more deeply.

Although these experiments indicate that FMR1 expression clearly influences sleep, unraveling the precise biological mechanism behind this connection may be challenging because FMRP controls the synthesis of many different proteins in the brain.

“[FMRP] controls the expression of so many genes and proteins, it might be a little bit naïve to think that the effects on sleep are through dendritic morphology, though this is still our working hypothesis,” Cirelli says.

In some respects, these flies are poor models of people with fragile X syndrome. The study found that flies that lack FMRP spend an abnormally long time sleeping, whereas anecdotal reports have indicated that children with fragile X sleep less than healthy children.

“[I] don’t observe longer sleep duration for any children with fragile X or autism,” says **Beth Goodlin-Jones**, associate professor of clinical psychiatry at the University of California, Davis. Instead, she finds that children with fragile X or autism struggle to fall asleep, and then wake up during the night[6].

Researchers have conducted only a few sleep studies of fragile X, which are difficult to compare because they relied on different methods to measure sleep. Goodlin-Jones finds that the number of nighttime awakenings recorded in children depends on whether she observes videotapes of sleep or uses actigraphy, a method that tracks movement via a wristwatch-like device[7].

For instance, a researcher watching a videotape would probably spot a participant who woke up during sleep without moving, but actigraphy would miss that event.

Genetics also complicates a direct comparison between flies and humans. Nelson, who has developed animal models of fragile X, notes that humans have two other genes related to FMR1 — FXR1 and FXR2 — which may be able to compensate when FMR1 is lost. Flies don’t have these genes, however, so their loss of FMR1 may lead to a substantially different phenotype.

“When you take away the FMR1 in flies, there’s nothing to step in and help,” says Nelson. “So how directly you can compare the FMR1 flies to fragile X patients is up in the air.”

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