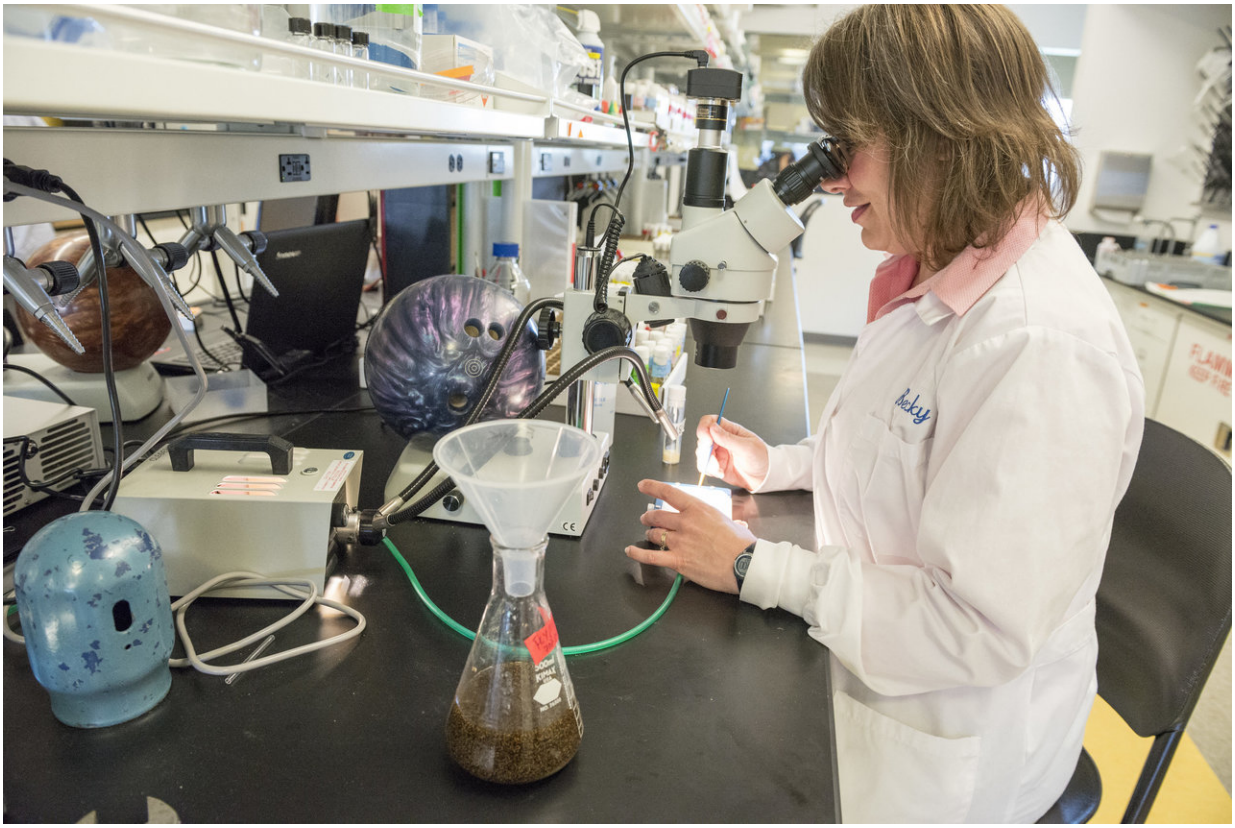
Researchers discover new clues on how sleep works in the brain

October 31 2018



Research technologist Becky Taylor uses a microscope to sort genetic strains of flies under anesthesia prior to placing them into vials for sleep studies. Credit: Cori Kogan, Washington State University Spokane

Star-shaped brain cells called astrocytes appear to play an essential role

in sleep, a new study by scientists from the Washington State University Sleep and Performance Research Center confirms. Published today in *PLOS Genetics*, their study shows that astrocytes communicate to neurons to regulate sleep time in fruit flies and suggests it may do the same in mammals, including humans.

This research has opened up new avenues to understanding how sleep works inside the brain, which may eventually help scientists answer the elusive question of why we sleep.

"We spend about a third of our lives asleep, and yet we don't really know why," said William Vanderheyden, the study's first author and an assistant research professor in the Elson S. Floyd College of Medicine. "Our work uses the fruit fly as a tool to identify mechanisms of sleep regulation that might be conserved across species—from fruit flies all the way to humans—so we might someday understand the function and process of sleep and could develop therapies to alleviate the burden of sleep loss."

Until recently, astrocytes—a type of glial cells that surround neurons, those energetic cells that communicate nerve signals between the brain and the body—were largely overlooked by scientists, who thought of glial cells as the mere "glue" that holds the brain together. However, recent findings by WSU scientists and others have suggested that astrocytes are more active than they seem and may somehow be involved in regulating sleep.

In their study, the WSU team combined that idea with recent knowledge about TNF-alpha, a protein involved in inflammation that has been shown to play a critical role in sleep regulation in humans and other mammals. They used fruit flies because their short life span and their genetic make-up—which is surprisingly similar to that of humans—make them an especially powerful tool for studying genetics.

"Fruit flies happen to have a molecule that is very similar to TNF-alpha that is called Eiger, and the receptor to which it binds is called Wengen," Vanderheyden said. "What we tried to identify through this research were mechanisms by which Eiger and Wengen could be regulating sleep in the fruit fly."

First, they bred a generation of flies in which the gene that controlled Eiger was switched off. These flies slept less overall, and their sleep was also more fragmented. Subsequently, they further manipulated the flies so that Eiger was switched off in specific brain cell types—either astrocytes or neurons. They saw a similar reduction in sleep in flies with Eiger switched off in astrocytes, whereas sleep duration in flies with Eiger switched off in neurons did not change. This suggested that Eiger contributes to the regulation of sleep time in a way that depends on astrocyte signaling, Vanderheyden said.

Next, they injected human TNF-alpha in both wild-type flies and Eiger mutants and found that, in both groups of flies, it increased sleep, as it had been previously shown to do in mammals.

Finally, they did an experiment in which they switched off Wengen—Eiger's receptor—in either astrocytes or neurons and measured sleep time in these flies after 12 hours of sleep deprivation, which normally leads to an increase in sleep known as rebound sleep. There was no change in sleep time in flies that had the Wengen receptor switched off in astrocytes, versus control flies. However, flies with Wengen switched off in neurons showed a significant reduction in sleep rebound. What's more, injecting human TNF-alpha into flies that had Wengen switched off in neurons did not increase sleep.

"This suggests that this signal from Eiger is going from astrocytes to neurons to drive sleep, which is a new finding," said Jason Gerstner, assistant research professor in the Elson S. Floyd College of Medicine

and senior author. "This generates a new hypothesis about the way we think sleep may be regulated in higher-order animals, including humans."

Next, Vanderheyden and Gerstner plan to take their hypothesis into mammals by studying whether the same astrocyte-to-neuron pathway regulates sleep in rodents. They are also interested in looking at this pathway in a fruit fly model of Alzheimer's disease, which is associated with both sleep loss and astrogliosis, an abnormal increase in astrocyte numbers caused by destruction of nearby neurons.

More information: *PLOS Genetics* (2018). DOI: 10.1371/journal.pgen.1007724

Provided by Washington State University