Researchers find molecular key to exhaustion following sleep deprivation

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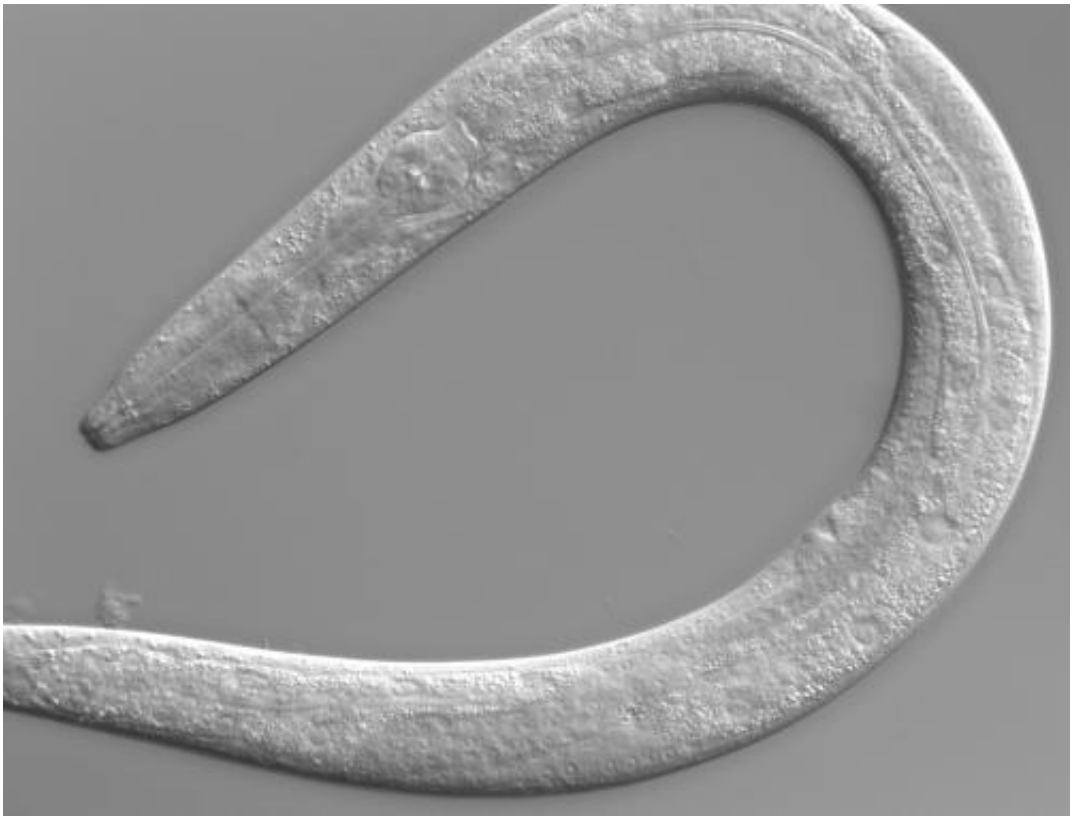

David Raizen, M.D., Ph.D., assistant professor of Neurology in the Perelman School of Medicine at the University of Pennsylvania, and his colleagues report in *Current Biology* that even in *Caenorhabditis elegans*, a tiny nematode worm that feeds on bacteria, loss of sleep is "stressful." Credit: David Raizen/Penn Medicine

It happens to everyone: You stay up late one night to finish an

assignment, and the next day, you're exhausted. Humans aren't unique in that; all animals need sleep, and if they don't get it, they must make it up.

The biological term for that pay-the-piper behavior is "sleep homeostasis," and now, thanks to a research team at the Perelman School of Medicine, University of Pennsylvania, one of the molecular players in this process has been identified – at least in nematode round worms.

David Raizen, MD, PhD, assistant professor of Neurology, and his colleagues report in Current Biology that even in Caenorhabditis elegans, a tiny nematode worm that feeds on bacteria, loss of sleep is "stressful."

The researchers forced the animals to stay awake during a developmental stage when they normally sleep, called "lethargus." These sleep-deprived worms, like college students after an all-nighter, exhibited signs of sleep homeostasis – they were harder to wake up compared to control worms.

While nematode worms do not sleep as vertebrates do, lethargus is a sleep-like state, says Raizen, characterized by episodic reversible immobility, elevated arousal thresholds, and homeostasis.

On the molecular level, loss of sleep in the worm was associated with migration of the stress-related DNA-binding protein DAF-16, also called FOXO, from the cell cytoplasm into the nucleus. Here, the protein activates expression of stress-related genes. Knocking out that DAF-16 gene eliminated the animals' homeostatic response – the equivalent of giving an up-all-night college student a free pass on sleep deprivation.

"You might think that is a good thing," Raizen says, "but a good percentage of DAF-16 mutants died" – as many as half of the worms in some cases. That, Raizen says, suggests that the movement of DAF-16 into the nucleus is not merely a consequence of sleep deprivation, but rather a key to the homeostatic response.

"There's something important about being able to mount a homeostatic behavioral response," Raizen concludes. "We don't know what that is, but it's clearly important to the animal."

Sleep homeostasis is critical to human health. Sleep deprivation in humans has been linked to weight gain and insulin resistance, and in laboratory rats, has been linked to death, Raizen says.

Whether DAF-16/FOXO will play the same role in humans as in nematodes is an open question. But it turns out that *C. elegans* is actually a useful model organism for studying vertebrate neurobiology, Raizen says. Many key observations made in the invertebrate have carried over to vertebrate systems.

Interestingly, when the team asked which tissue requires DAF-16 activity in order to restore sleep homeostasis in mutant animals, they found to their surprise that it isn't neurons. But restoring DAF-16 activity in muscle tissue did restore homeostasis, suggesting an extra-neuronal component of sleep.

"The muscle must somehow communicate with the nervous system to coordinate this response," Raizen says.

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