Circadian clock plays unexpected role in neurodegenerative diseases

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In a study of a fruit fly model of Huntington's disease, researchers found that jet lag protected the flies' brains from the disease. Credit: Sanjay Acharya

While your body might bemoan the many uncomfortable effects of jet lag, your brain may be thanking you for that cross-time zone travel.

In a new study, Northwestern University researchers induced jet lag in a fruit fly model of Huntington disease and found that jet lag protected the flies' neurons. The team then identified and tested a circadian clock -controlled gene that, when knocked down, also protected the brain from the disease.

The findings reveal potential new treatment pathways to slow the progression of or prevent neurodegenerative diseases.

"It seems counterintuitive, but we showed that a little bit of stress is good," said Northwestern's Dr. Ravi Allada, a circadian rhythms expert who led the research. "We subtly manipulated the circadian clock, and that stress appears to be neuroprotective."

The study will be published April 2 in the journal *Cell Reports*. Allada is the Edward C. Stuntz Distinguished Professor and chair of the department of neurobiology in Northwestern's Weinberg College of Arts and Sciences.

Patients with neurodegenerative diseases often experience profound disruptions in their circadian rhythms, or sleep-wake cycles. They may sleep more than usual or lose the ability to stay asleep. This can lead to nighttime wandering, increased agitation, general stress and a decreased quality of life.

"We have long known that a disrupted clock is an early indicator of neurodegenerative disease," Allada said. "In many cases, sleep disruption precedes any other symptom. But we didn't know whether the circadian disruption is a cause of the disease or a consequence of the disease."

To probe this question, Allada employed the fruit fly model of Huntington disease, a well-studied model organism for both circadian rhythms and neurodegenerative diseases. Although fruit flies might seem

completely different from humans, the neurons that govern flies' sleep-wake cycles are strikingly similar to humans'. Fruit flies that have the mutant Huntington gene also demonstrate similar symptoms as humans with the disease: reduced lifespan, motor deficits, neurodegeneration, disrupted circadian rhythms and an accumulation of diseased proteins in the brain, which aggregate and cause neurons to die.

"Normally, fruit flies wake up, get very active, then go to sleep and become inactive," Allada explained. "It's a 24-hour pattern. In the Huntington model, there is no rhythm. The flies wake up and fall asleep all the time."

Allada's team altered the flies' circadian rhythms two different ways. For one group of flies, the researchers altered the flies' environment by changing the daily timing of light-dark cycles. This manipulation caused the flies to live a 20-hour day instead of a 24-hour day. And for another group of flies, the researchers mutated a gene that is well known for controlling the internal circadian clock.

"We essentially gave the flies jet lag for every day of their lives," Allada said. "It's like traveling four hours east every day."

In both cases, the mutant Huntington disease proteins aggregated less and fewer neurons died. Allada, who expected jet lag to inflict even more damage on the brain, was surprised. "We had wondered if the clock played a role in the disease," he said. "It turned out that the clock was important—but in a manner that we did not predict."

Allada and his team were so fascinated by the result that they took the study one step further. They decided to screen through dozens of clock-controlled genes to pinpoint one that also might similarly protect the brain against neurodegenerative diseases.

The team zeroed in on a gene that encodes the "heat shock organizing protein," or "hop" for short. Not only is hop controlled by the body's circadian clock, the gene is also responsible for protein folding. Because misfolded proteins can result in many different neurodegenerative diseases, Allada thought hop made an interesting target. He and his team knocked down the hop gene in flies with the protein that causes Huntington disease and—again—were surprised. Knocking down the gene restored the flies' arrhythmic circadian clocks, reduced the aggregation of diseased proteins in the brain and reduced the number of neurons killed by those proteins.

"We thought that inhibiting this gene that helps your proteins fold properly would make things worse, but they got better," Allada said. "It again shows that a little bit of stress is probably good."

Next, Allada plans to test this method in a fruit fly model of Alzheimer's disease. He believes that targeting and knocking down the hop gene could potentially be an early intervention for slowing the progression of various neurodegenerative diseases.

Provided by Northwestern University

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