A Surprise about Our Body Clock

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The first gene known to control the internal clock of humans and other mammals works much differently than previously believed, according to a study by Utah and Michigan researchers.

The surprising discovery means scientists must change their approach to designing new drugs to treat jet lag, insomnia, some forms of depression, sleep problems in shift workers and other circadian rhythm disorders, according to researchers at the University of Utah's Huntsman Cancer Institute and the University of Michigan, Ann Arbor.

The study – which involved the so-called tau mutation that causes hamsters to have a 20-hour day instead of a 24-hour day – will be published online the week of July 3 in the journal *Proceedings of the National Academy of Sciences*.

The researchers discovered that what was previously believed about the tau mutation – that a decrease in gene activity sped up a mammal's internal clock – was incorrect. Instead, the mutation caused an increase in gene activity to speed up the clock, making the day two to four hours shorter for affected animals.

Previous work had indicated that the tau mutation occurred in a gene called casein kinase 1 epsilon (CK1) and that the mutation caused an 85 percent loss of gene activity. This, it was thought, explained why the hamster had a short day. But as it turns out, this idea was wrong.

"The key to developing treatments for problems like depression and insomnia – disorders influenced by circadian rhythm – is being able to predict how the body"s internal clock can be controlled," says David Virshup, M.D., co-principal investigator on the project and a Huntsman Cancer Institute investigator. "If the working model is wrong, drugs will have the opposite effect."

The new study involved the collaboration between University of Michigan mathematician Daniel Forger, Ph.D., assistant professor of mathematics, who had developed a computer simulation of the biological clock, and Virshup, who had previously done research on CK1's effect on circadian rhythm and its role in cancer development. Disruption of circadian rhythms has been linked to cancer and diabetes as well as depression and sleep disorders.

Forger ran computer simulations of how the tau mutation influenced the mammalian body clock. The tau mutant hamster has a short day. When a simulation used the prevailing theory that the mutation decreased CK1 gene activity, the simulation predicted that the day for the hamster got longer. But when Forger ran a simulation based on the controversial idea that the tau mutation increased activity of the CK1 gene, the day did get shorter, just as it does in real hamsters with the tau mutation.

"So he concluded that the tau mutation must increase, not decrease, the activity of the CK1 gene," contrary to the accepted wisdom, Virshup says.

Few people working in circadian rhythm were convinced that Forger's mathematical model was correct. But the Huntsman Cancer Institute researchers were interested because their experiments also suggested the tau mutation increased rather than decreased activity of the CK1 gene.

Virshup, with members of his lab Monica Gallego, Ph.D.; Erik Eide, Ph.D.; and Margaret Woolf, had used a drug that inhibited CK1 on cultured rat cells. According to the published research, they expected the cells to have a shorter day, just like the mutant hamster. Instead, the cells had a longer day. They were ready to believe that Forger's simulation could be proved.

A simple experiment showed them why the cells' day got longer and why Forger's simulation was correct.

The Virshup lab had already established a way to

measure how quickly PER, one of the proteins responsible for running the biological clock, degraded. It is the disappearance of PER and a related protein from cells that resets the body's internal clock to start a new day.

Forger's simulation said the tau mutation would cause PER to go away more quickly. The old model said the mutation caused PER to build up more quickly. Virshup explains: "The mutation can't do both. We put either the normal or the mutant CK1 gene into mouse cells, and then we watched what happened to PER stability."

The results proved Forger's prediction: the circadian rhythm within the mouse cells sped up because the mutant CK1 gene was more active, making the PER protein disappear more quickly. That would explain why a day for an animal with the tau mutation would last only 20 hours.

Virshup says his team has begun development of a mouse model so they can begin to test ways to regulate circadian rhythm based on their findings. That will be a necessary step before new drugs can be developed for disorders related to circadian rhythms.

Source: University of Utah