New pattern in our biological clock overturns long-held theory

October 8 2009

(PhysOrg.com) -- University of Michigan mathematicians and their British colleagues say they have identified the signal that the brain sends to the rest of the body to control biological rhythms, a finding that overturns a long-held theory about our internal clock.

Understanding how the human biological clock works is an essential step toward correcting sleep problems like insomnia and jet lag. New insights about the body's central pacemaker might also, someday, advance efforts to treat diseases influenced by the internal clock, including cancer, Alzheimer's disease and mood disorders, said University of Michigan mathematician Daniel Forger.

"Knowing what the signal is will help us learn how to adjust it, in order to help people," said Forger, an associate professor of mathematics and a member of the U-M's Center for Computational Medicine and Bioinformatics. "We have cracked the code, and the information could have a tremendous impact on all sorts of diseases that are affected by the clock."

The body's main time-keeper resides in a region of the central brain called the suprachiasmatic nuclei, or SCN. For decades, researchers have believed that it is the rate at which SCN cells fire electrical pulses---fast during the day and slow at night---that controls time-keeping throughout the body.

Imagine a metronome in the brain that ticks quickly throughout the day, then slows its pace at night. The rest of the body hears the ticking and adjusts its daily rhythms, also known as circadian rhythms, accordingly.

That's the idea that has prevailed for more than two decades. But new evidence compiled by Forger and his colleagues shows that "the old model is, frankly, wrong," Forger said.

The true signaling mechanism is very different: The timing signal sent from the SCN is encoded in a complex firing pattern that had previously been overlooked, the researchers concluded. Forger and U-M graduate student Casey Diekman, along with Dr. Mino Belle and Hugh Piggins of the University of Manchester in England, report their findings in the Oct. 9 edition of *Science*.

To test predictions made by Forger and Diekman's mathematical model, the British scientists collected data on firing patterns from more than 400 mouse SCN cells. The U-M scientists then plugged the experimental results into their model and found that "the experimental data were almost exactly what the model had predicted," Forger said.

Though the experiments were done with mice, Forger said it's likely that the same mechanism is at work in humans, since timekeeping systems are similar in all mammals.

The SCN contains both clock cells (which express a gene call per1) and non-clock cells. For years, circadian-biology researchers have been recording electrical signals from a mix of both types of cells. That led to a misleading picture of the clock's inner workings.

But Forger's British colleagues were able to separate clock cells from non-clock cells by zeroing in on the ones that expressed the per1 gene. Then they recorded electrical signals produced exclusively by those clock cells. The pattern that emerged bolstered the audacious new theory.

"This is a perfect example of how a mathematical model can make predictions that are completely at odds with the prevailing views yet, upon further experimentation, turn out to be dead-on," Forger said.

The researchers found that during the day, SCN cells expressing per1 sustain an electrically excited state but do not fire. They fire for a brief period around dusk, then remain quiet throughout the night before releasing another burst of activity around dawn. This firing pattern is the signal, or code, the brain sends to the rest of the body so it can keep time.

"The old theory was that the cells in the SCN which contain the clock are firing fast during the day but slow at night. But now we've shown that the cells that actually contain the clock mechanism are silent during the day, when everybody thought they were firing fast," Diekman said.

Piggins said the findings "force us to completely reassess what we thought we knew about electrical activity in the brain's circadian clock." In addition, the results demonstrate the importance of interdisciplinary collaborative research, he said.

"This work also raises important questions about whether the brain acts in an analog or a digital way," Belle said.

Provided by University of Michigan (news : web)