Biologists uncover dynamic between biological clock and neuronal activity

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Biologists at New York University have uncovered one way that biological clocks control neuronal activity—a discovery that sheds new light on sleep-wake cycles and offers potential new directions for research into therapies to address sleep disorders and jetlag.

"The findings answer a significant question—how biological clocks drive the activity of clock neurons, which, in turn, regulate behavioral rhythms," explained Justin Blau, an associate professor in NYU's Department of Biology and the study's senior author.

Their findings appear in the *Journal of Biological Rhythms*.

Scientists have known that our biological clocks control neuronal activity . But not previously understood is how this process occurs—that is, how does information from biological clocks drive rhythms in the electrical activity of pacemaker neurons that, in turn, drives daily rhythms?

To understand this mechanism, the researchers examined the biological, or circadian, clocks of Drosophila fruit flies, which are commonly used for research in this area. Earlier studies of "clock genes" in fruit flies allowed the identification of similarly functioning genes in humans.

In their study, the researchers focused on eight master pacemaker neurons located in the central brain—these neurons set the timing of the daily transitions between sleep and wake in the fly. Specifically, they were able to isolate these neurons from animals and identify sets of genes differentially expressed between dawn and dusk.

In a series of follow-up experiments, they concentrated on one gene, Ir, whose expression was found to be much higher at dusk than at dawn and much more highly expressed in pacemaker neurons than in the rest of the brain. Ir encodes a potassium channel that helps set the resting state of neurons – and so its rhythmic expression makes it an excellent candidate to help link the biological clock to pacemaker neuron activity. High levels of Ir expression at dusk should make it much harder for pacemaker neurons to signal than the low levels seen at dawn, a finding that fits with earlier studies showing that pacemaker neurons fire more at dawn than at dusk.

The authors also found that genetic manipulations that either increase or decrease Ir levels affect behavioral rhythms. Perhaps more interestingly, these were also associated with changes in the timing and strength of oscillations in the core clock.

"Biology is never as simple as we imagine it will be," explained Blau. "We were looking for an output of the biological clock that would link the core clock to neuronal activity. Ir seems to do this, but it also, remarkably, feeds back to regulate the core clock itself. Feedback loops seem to be deeply engrained into the biological clock and presumably help these clocks work so well."

Provided by New York University

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