Researchers uncover new ways sleep-wake patterns are like clockwork

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Researchers at New York University and Albert Einstein College of Medicine of Yeshiva University have discovered new ways neurons work together to ease the transition between sleep and wakefulness. Their findings, which appear in the journal *Neuron*, provide additional insights into sleep-wake patterns and offer methods to explore what may disrupt them.

Their study explored the biological, or circadian, clocks of Drosophila fruit flies, which are commonly used for research in this area. This is because it is relatively easy to find mutants with malfunctioning biological clocks and then to identify the genes underlying the altered behavior. Such studies in fruit flies have allowed the identification of similar "clock genes" in mammals, which function in largely the same manner as they do in a fly's clock.

In the Neuron study, the researchers moved up a level to study how pacemaker clock neurons—which express clock genes—interact with each other. Specifically, they looked at the relationship between master pacemaker neurons, which control the overall pace of the circadian system, and non-master pacemaker neurons, whose role in circadian rhythms has been less clear.

To do so, they examined flies with normally functioning master and non-master clock neurons and compared them with mutant flies in which the signaling of these neurons was either increased or decreased. These comparisons allowed the researchers to isolate the individual roles of these neurons and, in particular, to understand how master and non-master pacemaker neurons work together to control circadian rhythms.

Their results revealed a previously unknown role for non-master pacemaker neurons. Specifically, these neurons employ a neurotransmitter, glutamate, which suppresses signaling of the master pacemaker neurons during the evening. Artificially increasing this suppression by the non-master clock neurons in the morning made it much harder for flies to wake up. So in normal flies, these non-master pacemaker neurons have to stand aside at dawn, allowing the master pacemaker neurons to fire to wake up the fly. The authors concluded that the balance between signaling of these two groups of clock neurons helps to set the precise time of the transition between sleep and wakefulness.

"Our work shifts the emphasis away from clock genes and starts to address how clock neurons function in a neural network to regulate behavior," explained Justin Blau, an associate professor in NYU's Department of Biology and one of the study's co-authors. "And it shows the importance of studying individual groups of clock neurons, since different subsets can have opposite effects on animal behavior."

"This work helps to elucidate the neurotransmitters and receptors that facilitate communication between specific groups of nerve cells that regulate circadian rhythm," said co-author Myles Akabas, professor of Physiology & Biophysics and of Neuroscience at Albert Einstein College of Medicine. "It demonstrates the power of collaborative interdisciplinary research to address the molecular and cellular basis for behavior."

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