Networking around the clock

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A Brandeis University study published in *Cell* this week shows for the first time experimentally that the circadian cells in fruit flies function as a network that enables the insects to adapt their behavior according to seasonal changes. This discovery leads the way to understanding how mammals, and presumably humans, adjust physiology and behavior to environmental changes such as short winter days and long summer ones.

For years, behavioral geneticists have known that specific brain cells in Drosophila fruit flies regulate the daily rhythmic behavior according to 24-hour endogenous clock machinery. But until now, scientists had offered only mathematical models to explain how fruit flies and other animals, including humans, adapt to seasonal changes such as fluctuating day length and temperature.

"In this study we show how the 24-hour intrinsic molecular clock can produce a variable output, so that it fits any seasonal condition," said lead author Dan Stoleru. "This is especially exciting because it gives us an understanding of how animals extract vital information from the environment to drive innate behavior such as reproduction, migration or hibernation."

Stoleru, a researcher in the pioneering National Center for Behavioral Genomics lab led by Michael Rosbash, explained that this property is provided by an adaptable brain circuit of oscillating neurons, capable of responding specifically to different environmental cues. Previous research by the same team in the lab of Michael Rosbash had already demonstrated that two groups of neurons, called morning cells and

evening cells, keep circadian time, regulating what fruit flies do morning and evening, day in and day out.

By genetically manipulating these groups of cells in this study, Stoleru and his colleagues discovered that the network is dominated by either one group, acting as the master clock, or the other, depending on day length and season. In the summer, the evening cells run the show; when the days become shorter, the morning cells take over.

"Both kinds of clock cells can be masters at different times," said Stoleru, likening the network to an alternating master-slave relationship. "The morning cells like darkness and they become the master clocks in winter, and the evening cells process light information, so they become the masters in the summer, though it all may happen gradually. We don't know how the switch from slave to master actually happens, but at some point, one type of cell appears to take full control."

The study also sheds light on a poorly understood relationship between depression and circadian rhythm. The authors concluded that shaggy, the Drosophila homologue of the human gene GSK-3, is a key part of the biochemical pathway that signals the light changes in the environment to the core clock. GSK-3 is also the target of lithium, a common medication used in a number of mood disorders, including seasonal affective disorder, or winter depression. Interestingly, phototherapy, which involves subjecting the patient to intense pulses of light, has been shown as another effective treatment for various forms of depression.

"The indication that GSK-3 is at the same time a mediator of light effect and a clock molecule in Drosophila raises interesting prospects for understanding the etiology of various mood disorders as well as the mechanisms underlying some of the therapies employed to compensate them," explained Stoleru.

Source: Brandeis University