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Changing the Circadian Clock with the Seasons

New research has revealed what keeps animals' internal clocks running on time through the long nights of winter, the long days of summer, and everything in between. The research, reported in the April 6, 2007, issue of *Cell*, shows that a specific network of brain cells is the key to synchronizing the circadian clock to environmental cues, and reveals an astonishing degree of flexibility within the system.

Howard Hughes Medical Institute investigator Michael Rosbash, who led the study, says the findings—gleaned from work on the fruit fly *Drosophila*—have broad implications for understanding how innate behaviors such as mating, migrating, and hibernating are stimulated by environmental cues. Dan Stoleru, the lead author of the *Cell* paper and a postdoctoral fellow in Rosbash's laboratory at Brandeis University, adds that the study reveals insights into possible causes of seasonal depression as well as other forms of mood disorders that respond to light therapy.

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— **Michael Rosbash**

The major implication of this paper is that it is the brain network that gives the circadian clock such great plasticity. This allows an animal to adapt to environmental change, which includes seasonality, but may include other less predictable events. We anticipate that a similar phenomenon takes place in mammals, including humans, said Rosbash.

Circadian clocks in living creatures usually operate on a time cycle that varies between 22 and 26 hours in artificially constant environments. Connections with the light-dark cycle of the external world make the cycle 24 hours. The human circadian clock tells us when to sleep and awaken and controls

important physiologies involving hormones, body temperature, heart function, and oxygen consumption. In the fruit fly, the circadian function appears important for regulating periods of activity, analogous to the human sleep-wake cycle. Fruit flies have two characteristic peaks of activity, one in the morning and the other in the early evening, and each is controlled genetically by a separate group of brain circadian cells.

Rosbash is a leader in the field of circadian research. For the past 25 years he has been defining the machinery that underlies the nearly universal pattern of circadian rhythms in insects, animals, and humans. He employs the tools of *Drosophila* genetics to understand how the circadian clock ticks and which master neural circuits underlie circadian activity patterns.

For the past several years, Rosbash's team has focused on these two groups of neurons known as morning cells and evening cells. Studies led by Stoleru showed that these two cell groups constitute the master network and represent a dual control system over the circadian clock. In the current study, Stoleru altered the expression of genes in the separate centers of this circuit and observed the flies' activity patterns under conditions of total light, total darkness, and different combinations of periods of light and dark. Notably, he found that a gene called *shaggy*, whose human equivalent GSK-3 is a target of lithium therapy for severe affective disorders, is critical to conveying the information on light change to the clock machinery.

While manipulating the circadian clock in his fruit flies, Stoleru says he found an intriguing relationship involving morning cells and evening cells. Rather than one cell group being the master control of the clock as scientists had assumed, the two cell groups take turns acting as master and slave. Specifically, morning cells become master during darkness and slave by day, while evening cells become slave at night and master by day.

Each day, Stoleru says, it is evening cells' job to register when darkness falls, while morning cells must take note of first light. As days shorten with winter, the circadian network responds biochemically to mark the change. It will then anticipate a shorter period of sunlight and a longer period of darkness in the following 24 hours. The same phenomenon occurs when days get longer and nights shorter, Stoleru says. In this way, the clock synchronizes daily to mark the seasons and respond almost immediately to changes in the environment.

So what happens in humans when something prevents the circadian clock from synchronizing with seasonal changes, or when something simply throws the clock out of sync with the outside world?

There is a likely relationship between depression and circadian rhythm, Stoleru said. In the worst kind of seasonal affective disorder, lithium is used as a therapy. Lithium is a mood stabilizer and acts by inhibiting *gsk3*, also known as *shaggy*, the gene I manipulated in this study, says Stoleru. One of the conclusions of the study is that GSK3 is part of the photo-entrainment pathway, connecting the clock to the light environment. The last piece of the puzzle is this: one effective treatment of seasonal—and even non-seasonal—affective disorders is exposure to specific doses of intense

light (sometimes combined with sleep deprivation). The paper does not study this relationship explicitly, as this was not at all our purpose. But the presence of all the factors in the mix is striking, and it may explain why phototherapy works.

The notion of plasticity or adaptability may also explain why the endogenous period of animals, including humans, is almost never exactly 24 hours, said Rosbash. A rigidly fixed period may be incompatible with accommodating variable photoperiods - 24 hours comes only with entrainment, the connection of the circadian clock to the precise 24 hour light-dark cycle.