

MARCH 30, 2000

## Researchers Identify Unique Circadian Rhythm Photoreceptor

When an animal is exposed to constant, intense light, the internal clock goes haywire, losing all sense of night and day. Fruit flies exhibit the same reaction, and humans are predicted to respond similarly. In the laboratories of Howard Hughes Medical Institute investigator Michael Rosbash and Jeffrey Hall at Brandeis University, however, there is a strain of mutant flies that maintains a steady clock when barraged with intense light.

---

"A hallmark of every experimental organism from fruit flies to mice is that intense, constant light causes the normal circadian rhythm to go into arrhythmia, to essentially go whacko."

— **Michael Rosbash**

---

The flies carry a crippled light-reactive pigment called a cryptochrome. Experiments by Rosbash and his colleagues now indicate that the fly cryptochrome dCRY is perhaps the only photoreceptor molecule through which light regulates the fly's circadian rhythm, the near-universal 24-hour biological clock that governs sleep and wakefulness, rest and activity, body temperature, cardiac output, and many other functions.

In an article published in the March 30, 2000 issue of the journal *Nature*, Rosbash, Hall and Patrick Emery at Brandeis University, and Ralf Stanewsky of the University of Regensburg in Germany, show that mutant flies, called *cry<sup>b</sup>* flies, that have a faulty cryptochrome gene dCRY exhibit an aberrant response to intense, constant illumination.

"A hallmark of every experimental organism from fruit flies to mice is that intense, constant light causes the normal circadian rhythm to go into arrhythmia, to essentially go whacko," said Rosbash.

"However, we found that these *cry<sup>b</sup>* mutants did not show such arrhythmia under constant light, as measured by their activity. If there were circadian

photoreceptors other than dCRY, then constant light should have produced such arrhythmia.

"To find that these flies remain rhythmic under constant light really starts to prove that dCRY is the major circadian rhythm photoreceptor in this organism because there are no other photoreceptors that can pick up the light signal and drive the clock into a non-functioning arrhythmia," he said.

The *cry<sup>b</sup>* mutant flies still present a significant mystery, Rosbash says, because they show the normal daily rhythmic cycle of light-dark activity, even with the presumably crippled photoreceptor molecules.

"One possibility is that there is still a bit of function left in the mutant *cry<sup>b</sup>* cryptochrome," he said. "Another possibility is that there remains another entrée route into the circadian system, but not a true circadian route. It may be that light entering the eyes tickles the internal biological clock with enough information about the outside world to keep it in step with the light-dark cycle."

Or, said Rosbash, the very appearance of a light signal may cause a "startle response" in the flies that is sufficient to set their internal biological clock to daytime.

The scientists' next efforts will be to identify fly mutants with potential defects in the pathway that links dCRY to the proteins within the central pacemaker. "By exploring other mutants that remain rhythmic in constant light, we may be able to identify proteins that are linkers between dCRY and the central clock mechanism.

"There is really very little evidence of how the dCRY protein actually connects to the clockwork mechanism governed by the genes *period*, *timeless*, *clock* and *cycle*," said Rosbash. "Presumably, there is some kind of conformational change in the dCRY protein when it absorbs a photon of light that somehow affects the clock mechanism. But the system is almost a black box at present."

According to Rosbash, applying findings about circadian photosensitivity in fruit flies to mammals is currently problematic because a mammalian circadian photoreceptor has not yet been identified. Mammalian cryptochrome molecules appear to be involved in the central clockwork mechanism, rather than in light-detection, he said.