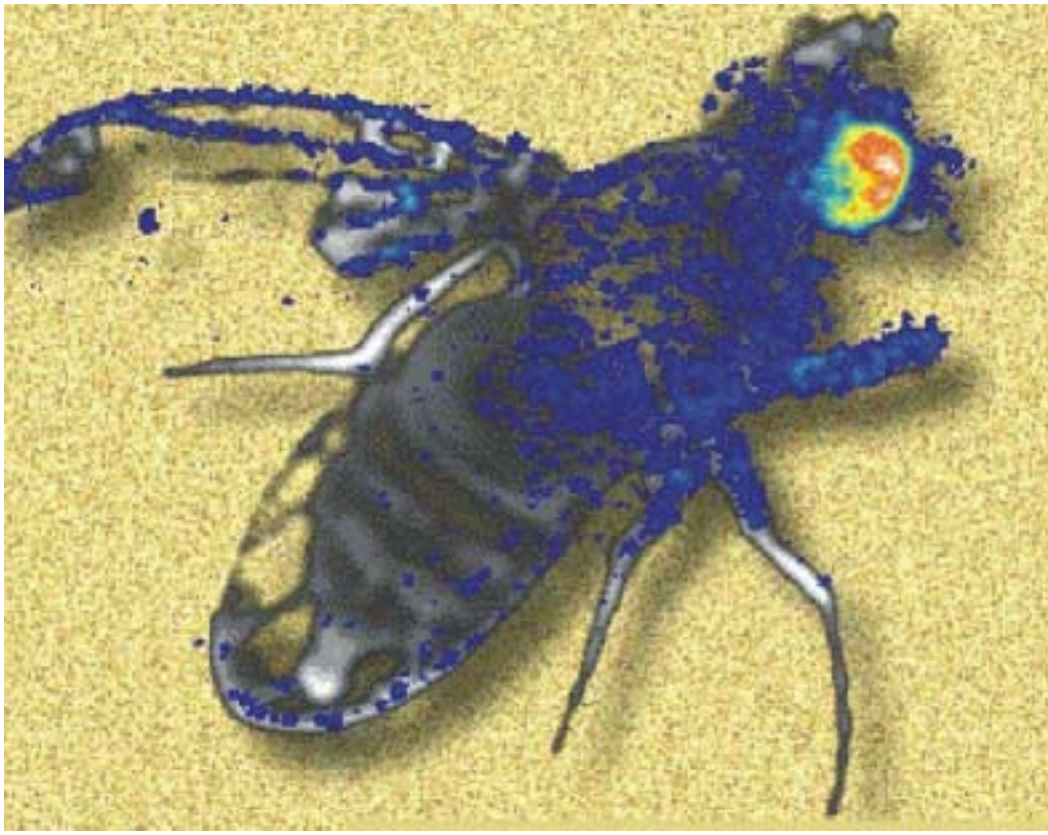
How Biological Clocks Work

Anyone who has traveled has experienced jet lag—that groggy realization that while your day is beginning in Washington, DC, the night you just left in San Francisco is hardly over. Jet lag is an inconvenient reminder that the body is set to a 24-hour clock, known by scientists as circadian rhythms, from the Latin *circa dies,* "about one day." An internal biological clock is fundamental to all living organisms, influencing hormones that play a role in sleep and wakefulness, metabolic rate, and body temperature.

Disruption of circadian rhythms not only affects sleep patterns but also has been found to precipitate mania in people with bipolar disorder (manic-depressive illness).[1] Other types of illnesses also are affected by circadian rhythms; for example, heart attacks occur more frequently in the morning while asthma attacks occur more often at night.[2,3]

Although biological clocks have been the focus of intensive research over the past four decades, only recently have the tools needed to examine the molecular basis of circadian rhythms become available. Early studies pointed to an area of the brain, the hypothalamus, as the location of the circadian pacemaker in mammals.[4] More recent findings show proteins called cryptochromes, located throughout the body, are also involved in detecting changes in light and setting the body's clock.[5]



Genes that code for the clock protein, PER, glow in the head and other body parts of a fruit fly. Researchers made the clocks glow by engineering transgenic strains of flies in which the same genes that illuminate a jellyfish and a firefly's tail are attached to PER. The gene for *luciferase,* the enzyme that glows intermittently in fireflies, was expressed along with PER to reveal when the clock protein was being produced. Flies were also molecularly altered to brightly mark the clock sites with Green Fluorescent Protein, which glows constantly in jellyfish. *Source: Jeffrey Plautz, Ph.D., Stanford University; Steve Kay, Ph.D., The Scripps Research Institute.*[6]

The first circadian gene was discovered in 1971 in the fruit fly;[7] a second circadian gene was detected 13 years later.[8,9] Following these discoveries, however, the search for clock genes in other organisms faltered. Not until

1997 was the first circadian gene found in a mammalian model, the mouse.[10] This discovery immediately accelerated the search for other clock genes, and findings in higher order animals are yielding a consistent picture of the role and function of circadian rhythms in organisms from bacteria to plants to mammals.[11]

Today, we know the most about the workings of the biological clock in the fruit fly and a peek inside its mechanisms illustrates the complex elegance of the rhythms of life.[12] The fly's clock consists of a core system of four regulatory proteins that interact to give the clock periodicity. The cycle begins when two of these proteins, CLOCK and CYCLE, bind together and increase the production of two other proteins, PER and TIM, the levels of which slowly accumulate over time. When enough PER and TIM are made, they inactivate the CLOCK-CYCLE complex, slowing their own production and signaling the end of the cycle.

Although parts of the puzzle still are missing, discoveries stimulated by this progress are yielding intriguing findings. Proteins such as DBT ("Double-Time") that act to fine tune the mechanism have been identified.[13] Recently, variations have been found in the human Clock gene, which may predispose people to be "early birds" or "night owls."[14] Other research has linked academic and behavior problems in adolescents to irregular sleep patterns.[15]

Researchers have found that imposing too early school start times on children requires unrealistic bedtimes to allow adequate time for sleeping.[16] Early school start times for adolescents are frequently associated with significant sleep deprivation, which can lead to academic, behavioral, and psychological problems, as well as increased risk for accidents and injuries, especially for teenage drivers. Completing our understanding of biological clockworks will lead to better treatments for diseases affected by circadian rhythm, as well as to methods of coping with disrupted sleep patterns.

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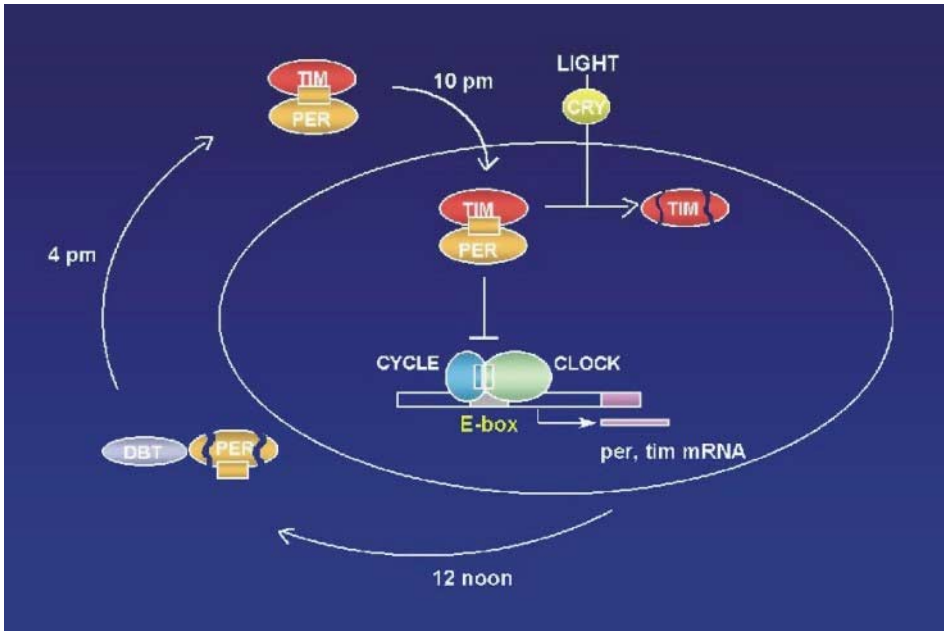

Fruit fly clock cycle - Interaction of four regulatory proteins, entrained by light, creates the daily rhythm of the fruit fly's clock. The binding of CYCLE and CLOCK turns on genes that make PER and TIM, which accumulate over several hours until they reach levels that turn off CYCLE and CLOCK. This, in turn, slows down the production of PER and TIM, which begins the cycle all over again. *Source: Steve Kay, Ph.D., and Karen Wager-Smith, Ph.D., The Scripps Research Institute.*[12]

References

[1] Leibenluft E, Albert PS, Rosenthal NE, et al. Relationship between sleep and mood in patients with rapid-cycling bipolar disorder. *Psychiatry Research,* 1996; 63(2-3): 161-8.

[2] Cannon CP, McCabe CH, Stone PH, et al. Circadian variation in the onset of unstable angina and non-Q-wave acute myocardial infarction (the TIMI III Registry and TIMI IIIB). *American Journal of Cardiology,* 1997; 79(3): 253-8.

[3] Jarjour NN. Circadian variation in allergen and nonspecific bronchial responsiveness in asthma. *Chronobiology International,* 1999; 16(5): 631-9.

[4] Pickard GE, Turek FW. The suprachiasmatic nuclei: two circadian clocks? *Brain Research,* 1983; 268(2): 201-10.

[5] Hall JC. Cryptochromes: sensory reception, transduction, and clock functions subserving circadian systems. *Current Opinion in Neurobiology,* 2000; 10(4): 456-66.

[6] Plautz JD, Kaneko M, Hall JC, et al. Independent photoreceptive circadian clocks throughout Drosophila. *Science,* 1997; 278(5343): 1632-5.

[7] Konopka RJ, Benzer S. Clock mutants of Drosophila melanogaster. *Proceedings of the National Academy of Sciences USA,* 1971; 68(9): 2112-6.

[8] Reddy P, Zehring WA, Wheeler DA, et al. Molecular analysis of the period locus in Drosophila melanogaster and identification of a transcript involved in biological rhythms. *Cell,* 1984; 38(3): 701-10.

[9] Bargiello TA, Jackson FR, Young MW. Restoration of circadian behavioural rhythms by gene transfer in Drosophila. *Nature,* 1984; 312(5996): 752-4.

[10] Antoch MP, Song EJ, Chang AM, et al. Functional identification of the mouse circadian Clock gene by transgenic BAC rescue. *Cell,* 1997; 89(4): 655-67.

[11] Liu Y, Heintzen C, Loros J, et al. Regulation of clock genes. *Cellular and Molecular Life Sciences,* 1999; 55(10): 1195-205.

[12] Darlington TK, Wager-Smith K, Ceriani MF, et al. Closing the circadian loop: CLOCK-induced transcription of its own inhibitors per and tim. *Science,* 1998; 280(5369): 1599-603.

[13] Kloss B, Price JL, Saez L, et al. The Drosophila clock gene double-time encodes a protein closely related to human casein kinase Iepsilon. *Cell,* 1998; 94(1): 97-107.

[14] Katzenberg D, Young T, Finn L, et al. A CLOCK polymorphism associated with human diurnal preference. *Sleep,* 1998; 21(6): 569-76.

[15] Wolfson AR, Carskadon MA. Sleep schedules and daytime functioning in adolescents. *Child Development,* 1998; 69(4): 875-87.

[16] Carskadon MA, Wolfson AR, Acebo C, et al. Adolescent sleep patterns, circadian timing, and sleepiness at a transition to early school days. *Sleep,* 1998; 21(8): 871-81.

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