

A Clock for the Ages

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The behavior of humans, like that of other animals, is characterized by precise 24-hour cycles of rest and activity, sleep and wakefulness. These cycles, termed a circadian rhythm, represent a fundamental adaptation of organisms to a pervasive environmental stimulus: the solar cycle of light and dark. Circadian rhythms are ubiquitous: present in prokaryotes and throughout the plant and animal kingdoms. They have two principal features: In the absence of a light-dark cycle, they oscillate with a period that differs from 24 hours (free-run), but in a normal solar cycle, they are entrained to the sun's stimulus with a period of exactly 24 hours. Circadian rhythms are genetically determined, and the free-running period is very similar among individuals of a single species, with little variation.

Humans have been presumed to be an exception to this rule. Studies have indicated that period may differ markedly among individuals, and it is thought that

the free-running period of human rhythms changes with age (1). This suggests that humans, unlike other animals, differ in the precision of their timekeeping. Just as we may be short or tall, lean or stout, fair or dark, perhaps our circadian clocks, too, are quite variable in their period. Czeisler and his colleagues set out to address these questions and to discover whether the period of circadian rhythms is precisely regulated in healthy, young humans and whether it alters with aging. Their data, reported on page 2177 of this issue, are both surprising and reassuring (2).

The characteristics of circadian rhythms yield insights into a neural system that provides circadian regulation in mammals. Rhythmicity is generated in the absence of external stimuli, indicating the presence of a circadian pacemaker that generates a circadian signal. The expression of circadian regulation indicates that the pacemaker is coupled to effector systems under circadian control, and entrainment by the light-dark cycle implies the presence of photoreceptors with connections to the pacemaker. The genetic determination of pacemaker function, including period, is evi-

dence that a set of molecular events constitutes a fundamental clock mechanism. This has been studied extensively over the last 15 years and we now have some understanding of the process. The basis of circadian function is transcription of clock genes (such as *tim* and *per*) and synthesis of the proteins they encode. Interactions among these proteins result in feedback inhibition of gene transcription. With degradation of the protein products, gene transcription is again initiated to reestablish the cycle (see the figure). The major components of the cycle have been identified and, although much remains to be established, the fundamental mechanisms appear conserved from fruit fly to human (3). These molecular events are coupled to a series of neuronal events, not well understood, that result in a circadian output signal. The basis for the neural signal appears to reside in regulation of cell membrane potential (4).

All of the available evidence indicates that there is one principal circadian pacemaker in mammals, the suprachiasmatic nucleus (SCN) of the hypothalamus. This small, paired nucleus situated just above the optic chiasm receives entraining information from a discrete subset of retinal ganglion cells through a direct retinohypothalamic tract (5). It also receives nonphotic input from other brain areas that modulate pacemaker function (6). The SCN exhibits

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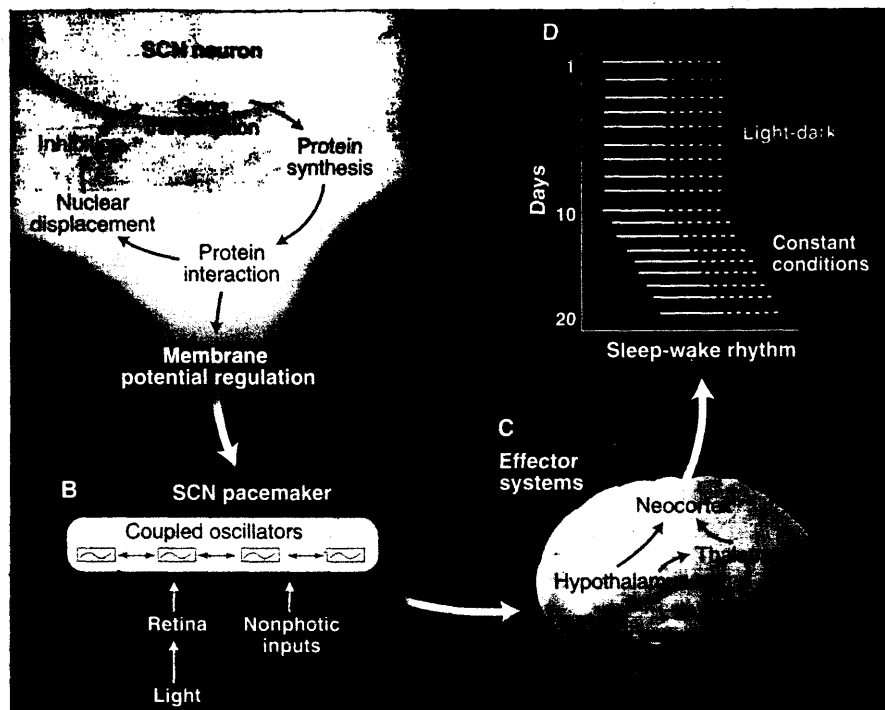
a rhythm in neuronal firing rate (4), the signal for the temporal organization of the sleep-wake cycle and other physiological and endocrine functions. Together these functions present a broad, rhythmic substrate for the successful elaboration of sleep, an essential behavioral state (7), and adaptive waking behavior. Destruction of the SCN results in a loss of the temporal organization of behavior (8), with sleep and wake occurring in normal amounts but randomly distributed over time. Similarly, rhythms in many other physiological and behavioral variables, including core body temperature, and plasma levels of corticoid hormones and melatonin, are also lost. Within the SCN, individual neurons appear to function as circadian oscillators that are coupled to form a pacemaker (9). The SCN projects to areas of the hypothalamus involved in neuroendocrine and sleep-wake regulation (8), and the SCN and its connections comprise a specific and distinct neural system, the circadian timing system (see the figure). The central feature of the system is the SCN, which generates a precise circadian signal regulated by photic and nonphotic input to the nucleus that is conveyed to effector systems under circadian control via SCN projections.

What have we learned about the human circadian timing system from the work of Czeisler and his colleagues? Studies prior to theirs have shown a free-running period of the rest-activity rhythm in humans ranging from 13 to 65 hours, with a mean around 25 hours. Studies of the daily oscillations in body temperature have provided estimates of period ranging from 24.2 to 25.1 hours (physiological measures in general give less variance than measurements of the sleep-wake cycle). Czeisler *et al.* (2) used a "forced desynchrony protocol" in which sleep-wake cycles are fixed at an arbitrarily long period of 28 hours with subjects maintained in an otherwise timeless environment. The 28 hour sleep-wake cycle does not entrain the SCN and the rhythms in core body temperature, cortisol and melatonin free-run throughout the study. Because the subjects have normal amounts of sleep, the experiment can be continued long enough, 28 to 39 days, to obtain precise measurements of the free-running period for each variable in each subject.

The data obtained are fascinating. First, the intrinsic period is exactly the same for each variable—melatonin, cortisol, and temperature—in the young subjects. Thus, SCN pacemaker control over each variable is precise. The intrinsic period of each variable is controlled with similar precision in the elderly, and the period of the pacemaker is essentially identical in young and elderly subjects. Thus, the timing of

the pacemaker is as precise in a group of individuals with ages between 64 and 74 as it is in a group with ages from 21 to 30. This is a surprise in view of the popular notion that the circadian period shortens with aging, resulting in fewer hours of

first rate. Second, this precision is maintained despite the many alterations in brain function that are associated with aging. This is a remarkable discovery: an important human function that does not deteriorate with age. From this, we can



Sleeping easy. The organization of the circadian pacemaker. Circadian rhythms are genetically determined through gene expression in a feedback loop which, in mammals, occurs in neurons of the suprachiasmatic nucleus (SCN) (A). These neurons are individual oscillators that are coupled to form a pacemaker (B), which is connected to effector systems under pacemaker control (C). For the sleep-wake cycle the effector system is the neocortex, which receives critical input from the hypothalamus and thalamus (D). In the upper right-hand corner, the behavioral sleep-wake rhythm is shown entrained for 10 days (solid line represents waking, dashed line, sleep) in a light-dark cycle, and free-running with a period greater than 24 hours under constant light conditions.

sleep and early morning awakening. Interestingly, the aged subjects did report an advance in phase of their rest-activity rhythm in their normal environment, and one assumes that this would hold true for temperature, melatonin, and cortisol as well. Clearly this cannot be attributed to a shortening of the length of the free-running period in the circadian pacemaker, but more likely reflects an age-related alteration in the mechanisms of pacemaker entrainment. Whether this alteration is in the retinohypothalamic pathway or within the clock itself remains to be determined.

The Czeisler report, then, gives us three important insights. First, it tells us that the period of the human SCN circadian pacemaker is precisely controlled. In this, it does not differ from circadian pacemakers in other mammals that have been studied extensively. Regardless of other differences between us, our clocks are extremely similar and our timing is

make the third inference: Precise circadian timing must be important to the health and adaptation of humans. Clearly, nature would not go to the trouble of constructing such an elegant, functional, and durable timepiece if it was not critical to us throughout our lives. With these data we can now look forward to a better understanding of disorders of circadian timing in both the young and the old.

References

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