Effect of Light on Human Circadian Physiology

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KEYWORDS

• Biological rhythm • Core body temperature
• Illuminance • Melatonin • Phase-response curve

Circadian rhythms are variations in physiology and behavior that persist with a cycle length close to 24 hours even in the absence of periodic environmental stimuli. It is hypothesized that this system evolved to predict and therefore optimally time the behavior and physiology of the organism to the environmental periodicity associated with the earth's rotation. Because the cycle length, or period, of this endogenous timing system is near, but not exactly, 24 hours in most organisms, circadian rhythms must be synchronized or entrained to the 24-hour day on a regular basis. In most

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organisms, this process of entrainment occurs through regular exposure to light and darkness.

Early reports from studies of human circadian rhythms had suggested that humans were unlike other organisms, being relatively insensitive to light and more sensitive to social cues to entrain their circadian systems. However, subsequent studies, and reanalysis of results from those early studies, have found that the human circadian system is like that of other organisms in its organization and in its response to light, and is as sensitive to light as the circadian systems of other diurnal organisms. In this article, we review the results of studies over the past 25 years conducted in our laboratory and in those of others investigating the effects of light on the human circadian timing system.

NEUROANATOMY OF THE MAMMALIAN CIRCADIAN SYSTEM

Studies published in the early 1970s established the suprachiasmatic nucleus of the hypothalamus as the central circadian pacemaker in mammals.[1–5] This pacemaker is composed of individual cells that, when isolated, can oscillate independently with a near-24-hour period.[5,6] The suprachiasmatic nucleus receives direct input from the retina,[7–9] providing a mechanism by which entrainment to light-dark cycles occurs. Investigators have recently described a subset of retinal ganglion cells that serve as photoreceptors for circadian and other non–image-forming responses (NIFs).[10–12] These specialized retinal ganglion cells are distributed throughout the retina, project to the suprachiasmatic nucleus, are photosensitive, and contain melanopsin as their photopigment.[13,14] While the photosensitive retinal ganglion cells can mediate circadian responses to light, evidence suggests that rod and cone photoreceptors can also play a role in circadian responses to light.[15,16] The relative contribution of different photoreceptors to circadian responses is not yet well understood and is an area of intense research. It is likely that the intensity, spectral distribution, and temporal pattern of light can all affect the relative contribution of different photoreceptors to circadian responses. The same neuroanatomical features of the circadian system described in mammals are also present in humans.[17–24]

PHASE-DEPENDENT RESPONSE OF THE HUMAN CIRCADIAN SYSTEM TO LIGHT

Studies of the effects of light on the circadian system of insects, plants, and animals conducted from the late 1950s through the 1970s demonstrated that the timing of a light stimulus has an important influence on the direction and magnitude of response to that stimulus.[25–28] Those studies indicated that the circadian system of both nocturnal and diurnal organisms is most sensitive to light during the biological night. Because humans sleep throughout most of their biological night, testing the influence of light on the human circadian system requires that in the sleep-wake cycle be shifted to deliver the light stimulus at the time of highest expected sensitivity. Because of prior reports suggesting that social cues influenced human circadian rhythms, that manipulation of sleep-wake timing was a concern in the earliest human light studies.[29,30]

For those reasons, we therefore conducted one of our earliest studies of the effect of light on the human circadian system on a subject whose circadian temperature rhythm had an unusual phase relationship to her sleep-wake cycle.[31] We identified a subject whose sleep-wake cycle timing was fairly normal, but whose circadian core body temperature rhythm was several hours earlier than normal, resulting in much of her biological night occurring before the time she went to bed. In the experiment we conducted, the subject was exposed to several hours of light every evening for a week, and the timing of her rhythms of core body temperature and plasma cortisol were assessed before and after that week of evening light exposure. Both rhythms were shifted by approximately 6 hours, and examination of temperature data collected throughout the experiment suggested that the shift had already occurred after only 2 days.

This finding that light could have this rapid and strong effect on the timing of human circadian rhythms led us to conduct a series of studies in normal young adults to whom we applied a series of light stimuli over 2 to 3 days.[32,33] In those studies performed in the late 1980s, we held the intensity, spectral distribution, and duration of the light stimulus constant, but varied the time at which the initial stimulus was applied. To do this, we had to shift the timing of the sleep-wake cycle so as to be able to present light stimuli across the entire 24-hour circadian cycle. In the course of doing these initial experiments, we were attempting to produce a phase-response curve (PRC).[28]

Our results were not surprising in some ways, but surprising in others. We found that humans, like other organisms, are most sensitive to light stimuli during the biological night, and far less sensitive to light in the middle of the biological day.[32,34] We also found that when humans are exposed to a light stimulus in the late-biological-day/