PHYSIOLOGY

Absence of Circadian Phase Resetting in Response to Bright Light Behind the Knees

Kenneth P. Wright Jr.* and Charles A. Czeisler

Light is the dominant environmental time cue for circadian clocks. In 1998, bright, narrow-spectrum blue light exposure to the back of the knees was reported to reset the human circadian pacemaker (HCP) (*1*). *Science* recognized the widely cited report as among the top discoveries that year to "transform our ideas about the natural world" and reported that several groups had repeated the finding (*2*). Patented treatments for circadian sleep disorders followed (*3*, *4*).

Yet the report was challenged because humoral phototransduction via the circulatory system, which was cited as a mechanism that might mediate such a circadian resetting response (*5*), had never before been demonstrated to reset a circadian pacemaker in any organism (*6*). Moreover, uncontrolled aspects of the experiments were hypothesized as being responsible for the reported results (*7*, *8*). Indeed, in (*1*), subjects' eyes were exposed to low, but biologically active (*9*) light intensities during the illumination of the knees, thereby potentially confounding assessment of the response to light behind the knees. Furthermore, melatonin phase estimates were not provided for control subjects (*1*). Using a variety of different protocols, most other groups have since been unable to affect the HCP with dermal light exposure (*9*). Even Campbell and Murphy reported an inability to elicit phase advance shifts when subjects were asleep (*10*)—contrary to their initial expectations (*1*, *3*)—although they have reported that light to the back of the knees during sleep influenced another aspect of human brain function: REM sleep (*11*). Given the importance of this result to the fundamental understanding of the neurobiology of the HCP, we therefore set out to replicate the findings of (*1*).

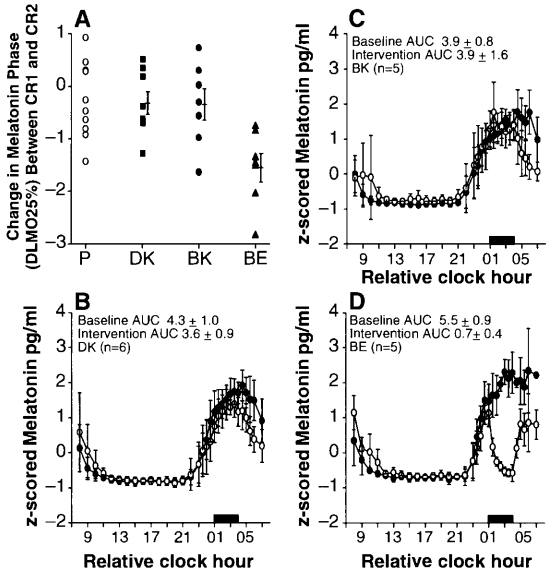

Fig. 1. (**A**) Phase shifts for groups DK, BK, and BE. For reference, column P illustrates the changes in phase projected from estimates of intrinsic circadian period (*9*). Lines represent mean ± SEM. (**B** to **D**) Melatonin data for conditions DK and BK were superimposable during the intervention time (solid bar) for the intervention night (○) and the previous night (●). BE significantly delayed melatonin phase and acutely suppressed melatonin secretion compared with DK controls (P = 0.003272) and (P = 0.000020), respectively. In contrast, there was no significant difference for melatonin phase changes between BK and DK and no acute melatonin suppression during the intervention in either of these conditions (P = 0.943071) and (P = 1.000000), respectively. Significant differences for phase shifts and melatonin suppression were also observed between BE and BK (P = 0.011359) and (P = 0.000016), respectively.

Twenty-two 10-day inpatient phase-resetting trials were conducted. Constant routines (*9*) were used to assess circadian melatonin phase before and after exposure to one of three 3-hour-long interventions balanced by gender: 0 lux ocular and behind the knee (DK), 0 lux ocular and up to 13,000 lux behind the knee (BK), and ~9,500 lux ocular and 0 lux behind the knee (BE). As in (*1*), we used the same device from the same manufacturer; subjects maintained a nighttime sleep schedule and were aroused from scheduled sleep for one episode of light-behind-the-knee exposure for the same duration of time and at the same light intensity reported to elicit a phase delay shift. Phase shifts were assessed two nights after the intervention. However, our study differed from (*1*) in several respects to ensure the precision of the phase estimates and to control for possible phase-shifting stimuli. First, participants were shielded from ocular light (0 lux) during extraocular light exposure. Second, condition assignments were double blind and random, with all light exposures at one circadian phase and each individual tested only once. Third, participants were maintained in very dim light (~1.5 lux in the angle of gaze) between circadian phase assessments during scheduled wakefulness preceding and after the intervention. Fourth, melatonin data were used to assess circadian phase in both active and control conditions (*9*). Finally, sleep was not extended.

In contrast to ocular light exposure, which significantly delayed melatonin phase and acutely suppressed melatonin secretion compared with controls, there was no significant difference for melatonin phase changes between subjects exposed to light behind the knee compared with controls and no acute melatonin suppression during the intervention (Fig. 1). The melatonin phase changes observed in groups DK and BK were consistent with the transient, period-dependent phase realignment expected in dim light (*12*) (Fig. 1A, column P). These data indicate that ocular light exposure was necessary and sufficient for both circadian phase resetting and the regulation of melatonin secretion. The current findings are inconsistent with the report that bright light exposure to the back of the knees can reset the HCP (*1*). Although nonocular light exposure can directly affect deep brain and body circadian oscillators in many species (*9*), the suggestion that photic signals are carried from the back of the knee to the human brain via the circulatory system is not supported by our data.

References and Notes

1. S. S. Campbell, P. J. Murphy, *Science* **279**, 396 (1998).
2. News and Editorial Staff, *Science* **282**, 2157 (1998).
3. S. S. Campbell, P. J. Murphy, U.S. Patent 6,135,117 (2000).
4. H. S. Seki, J. Perkins, U.S. Patent 6,164,787 (2000).
5. D. A. Oren, *Neuroscientist* **2**, 207 (1996).
6. R. G. Foster, *Neuron* **20**, 829 (1998).
7. S. Yamazaki, M. Goto, M. Menaker, *J. Biol. Rhythms* **14**, 197 (1999).
8. G. Atkinson, J. Waterhouse, T. Reilly, B. Edwards, *Chronobiol. Int.* **18**, 1041 (2001).
9. Supplementary material is available on *Science* Online.
10. S. S. Campbell, P. J. Murphy, *Sleep* **23**, A23 (2000).
11. P. J. Murphy, S. S. Campbell, *Am. J. Physiol.* **280**, R1606 (2001).
12. K. P. Wright Jr., R. J. Hughes, R. E. Kronauer, D.-J. Dijk, C. A. Czeisler, *Proc. Natl. Acad. Sci. U.S.A.* **98**, 14027 (2001).

13. We thank the participating volunteers; research staff; subject recruiters; S. Ma, M. Hines, and C. O'Brien; J. T. Hull for data analysis; J. M. Ronda and B. Cade for technical support; and the BWH investigational drug service for overseeing the double blind procedures. Supported by NIH R01-MH45130. The studies were performed in a General Clinical Research Center supported by NIH M01-RR02635. K.P.W. was supported by fellowships from the NIH (T32-DK07529), the Medical Foundation, and the Harold Whitworth Pierce Charitable Trust.

Supporting Online Material

www.sciencemag.org/cgi/content/full/297/5581/571/DC1
Methods
Fig. S1

Division of Sleep Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, 221 Longwood Avenue, Suite 438, Boston, MA 02115, USA.

*To whom correspondence should be addressed. E-mail: kwright@hms.harvard.edu