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COVER

El Misti Volcano, with city of Arequipa, Peru, in foreground. The lavas, together with those of the numerous stratovolcanoes along the Pacific coasts of North and South America, are predominantly andesite. Geochemical studies show that the El Misti lavas contain a component from rocks of the Precambrian basement on which the volcano sits. See page 1245. [G. R. Tilton, University of California, Santa Barbara]

The American Association for the Advancement of Science was founded in 1946 and incorporated in 1974. Its objects are to further the work of scientists, to facilitate cooperation among them, to foster scientific freedom and responsibility, to improve the effectiveness of science in the promotion of human welfare, and to increase public understanding and appreciation of the importance and promise of the methods of science in human progress.

patterns indicates the generality of these findings. This has formed the basis for the development by Kronauer *et al.* of a mathematical model of the human circadian timing system, using two interacting oscillators (16), that may correspond to specific anatomical structures within the human brain (17). The success of that mathematical model in reproducing the patterns observed (Fig. 1) supports our analysis of the data. These findings have major implications for understanding the timing of human sleep and may also help explain the sleep-wake patterns in shift workers and in certain clinical sleep disorders (18).

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- Double-plotting is the standard format for the presentation of circadian rhythm data of other species [C. P. Richter, *Biological Rhythms in Medicine and Psychiatry* (Thomas, Springfield, Ill., 1965)]. Yet, it has rarely been used correctly in the reporting of human rest-activity cycle data. When this technique was applied to the available data on human rest-activity patterns, the results proved remarkably consistent (3).
- When the length of the rest-activity cycle period was < 24 hours (5), the length of the waking episodes was also much shorter. Nonetheless, a cluster line of 6- to 10-hour sleep episodes continued to occur with their usual phase relation to the temperature rhythm. However, sleep episodes begun out of phase with the cluster line were now very short (< 4 hours) instead of very long (> 12 hours). Thus, prior wakefulness was only a factor in determining whether sleep episodes of abnormal length were very short or very long (9).
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- Supported in part by NIH grants MH-28460 and AG-00792 and by ONR contract N 00012-76-C-1071; by the NIH medical scientist training program (GM-07365) at Stanford Medical School (C.A.C.); by NIMH training grant MH-06418 (J.C.Z.); and by NIH career development award NS-00247 (M.C.M.-E). We thank the subject volunteers; the Laboratory of Human Chronophysiology data collection and preparation staff; C. Campbell, J. M. Cowan, J. Finkelstein, S. Haecker, J. Kraut, A. Laiosa, and D. Sadowick for help in the data analysis; J. Ronda for analytic computer programming; S. Borack, A. Grunther, S. Lawson, and R. H. Rubin for preparation of the figures; L. C. Kilham, K. Redding, and S. Willis for preparation of the manuscript; M. C. Carskadon for advice on quantifying alertness assessments; and H. E. Albers, C. Guilleminault, and W. C. Dement for suggestions regarding the manuscript.
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Light Suppresses Melatonin Secretion in Humans

Abstract. Bright artificial light suppressed nocturnal secretion of melatonin in six normal human subjects. Room light of less intensity, which is sufficient to suppress melatonin secretion in other mammals, failed to do so in humans. In contrast to the results of previous experiments in which ordinary room light was used, these findings establish that the human response to light is qualitatively similar to that of other mammals.

The physiology of the pineal gland and its hormone melatonin have been studied extensively in mammals (1). Both nocturnal and diurnal animals synthesize and secrete melatonin almost exclusively during nighttime darkness (2), a pattern consistent with the suppression of melatonin synthesis by environmental light (3). Even in constant darkness this 24-hour secretory rhythm persists (4), driven by an endogenous circadian oscillator in the suprachiasmatic nucleus (SCN) of the hypothalamus (5). A neuronal pathway links the SCN to spinal nuclei of sympathetic neurons that innervate the pineal gland (6). Neuronal input from the retina to the SCN (via the retinohypothalamic tract) mediates the suppressant effect of light and the entrainment of the melatonin secretory rhythm to the light-dark cycle (5).

Although in humans there is a nocturnal increase in melatonin secretion which appears to be mediated by sympathetic neurons (7), previous studies have failed to demonstrate a pronounced suppressant effect of light (8-11). Consequently, some investigators have proposed that the regulation of melatonin secretion in humans is substantially different from that of all other mammals (including nonhuman primates) and have speculated that escape from direct control by the environmental light-dark

cycle has conferred on humans an evolutionary advantage (12). We examined this apparent difference and report that light of higher intensity than that used in previous studies unequivocally suppresses melatonin secretion in humans.

Six normal subjects (four females and two males), who gave written informed consent, were each studied on two separate occasions. Blood was sampled at intervals through an indwelling catheter. Between 11 p.m. and midnight on each night of the study the subjects retired to a dark room to sleep; at 2 a.m. they were awakened and exposed to light for 2 hours. On one night fluorescent light was used (Vita-Lite, ≈ 500 lux at eye level—the approximate intensity used in home or industrial conditions), and on another night incandescent light was used (150-W flood lamps, ≈ 2500 lux at eye level—the approximate intensity of indirect sunlight measured 1 inch from a window on a clear spring day). At 4 a.m. the subjects resumed sleeping in the dark. The two male subjects were studied under two additional conditions: on a third night they were exposed to approximately 1500 lux of incandescent light between 2 a.m. and 4 a.m., and on a fourth occasion they slept in the dark throughout the night (13). The concentration of melatonin in the plasma was assayed by gas chromatography-negative chemical ioni-

ization mass spectrometry method of Lewy and Marky (14).

Melatonin concentrations decreased 10 to 20 minutes after the subjects were exposed to 2500-lux incandescent light and reached near-daytime levels within 1 hour (Fig. 1). After the subjects resumed sleeping in the dark, the melatonin concentrations increased immediately and within 40 minutes were at the levels measured before exposure. The fluorescent light (500 lux) did not reduce melatonin, and there was no change after the return to darkness. In the two subjects who were exposed to 1500-lux incandescent light, melatonin concentrations decreased to levels intermediate between those measured during exposure to 500 and 2500 lux (Fig. 2). The return to normal nighttime concentrations after subjects were exposed to 1500 lux was similar to that occurring after their exposure to 2500 lux. The concentration of melatonin in subjects awakened and exposed to 500-lux fluorescent light did not differ significantly from that measured while they were asleep in the dark.

These data indicate that brief exposure to environmental light suppresses mel-

atonin secretion in humans. Inhibition of secretion appears to be immediate, since the rate of decline in melatonin corresponds to the half-life of the hormone in primate plasma (15). Since exposure to 1500 lux produced an intermediate decrease in melatonin, there may be a direct relation between the decrease in melatonin concentration and light intensity (16).

Humans seem to require light of considerably higher intensity for melatonin suppression than do other mammals (17). For example, Vita-Lite of less than 10 lux suppresses melatonin synthesis in rats 50 percent, and 500 lux is well above the intensity required for complete inhibition (18). The human response to light also differs from that of other species in another respect. When rats are briefly exposed to light during the second half of the night, melatonin synthesis remains suppressed after the return to darkness (19). In our human subjects melatonin concentrations quickly returned to normal nighttime levels. Thus a higher intensity of light may be required to suppress melatonin secretion in humans, and secretion may be more readily re-

sumed after the onset of darkness (20).

Earlier attempts to suppress melatonin secretion probably failed because the light was insufficiently intense (8-11, 21). The importance of intensity may have been underestimated, because of reports of substantial melatonin secretion in humans during the day—even during exposure to sunlight (11, 22, 23). Using mass spectral assay, however, we consistently found very low concentrations of melatonin during the day. Moreover, we have found that sunlight suppresses melatonin in subjects whose sleep has been delayed (24). The high daytime levels reported by previous investigators probably resulted from a lack of assay specificity.

One example of the many other effects of light on mammals is the photoperiodic regulation of reproductive cycles (25). Light may have significant endocrine effects on human beings as well. For example, and in northern Finland most conceptions occur during the summer (26) and infertility is more common in blind women (27). Our results are further evidence for an ocularly mediated effect of light on endocrine function in humans (28).

It appears that the same neuroanatomical pathways mediate melatonin secretion in humans as in other mammals (29). The recognition that humans require light of much higher intensity than other species for suppression of melatonin secretion should be helpful in future clinical investigations. Humans may also require brighter light for the entrainment of circadian rhythms [for example, the re-entrainment of circadian rhythms after air travel is retarded if the subjects are kept indoors (30)]. Perhaps, by distinguishing among different light intensities, humans have adapted to artificial lighting while remaining sensitive to the natural light-dark cycle.

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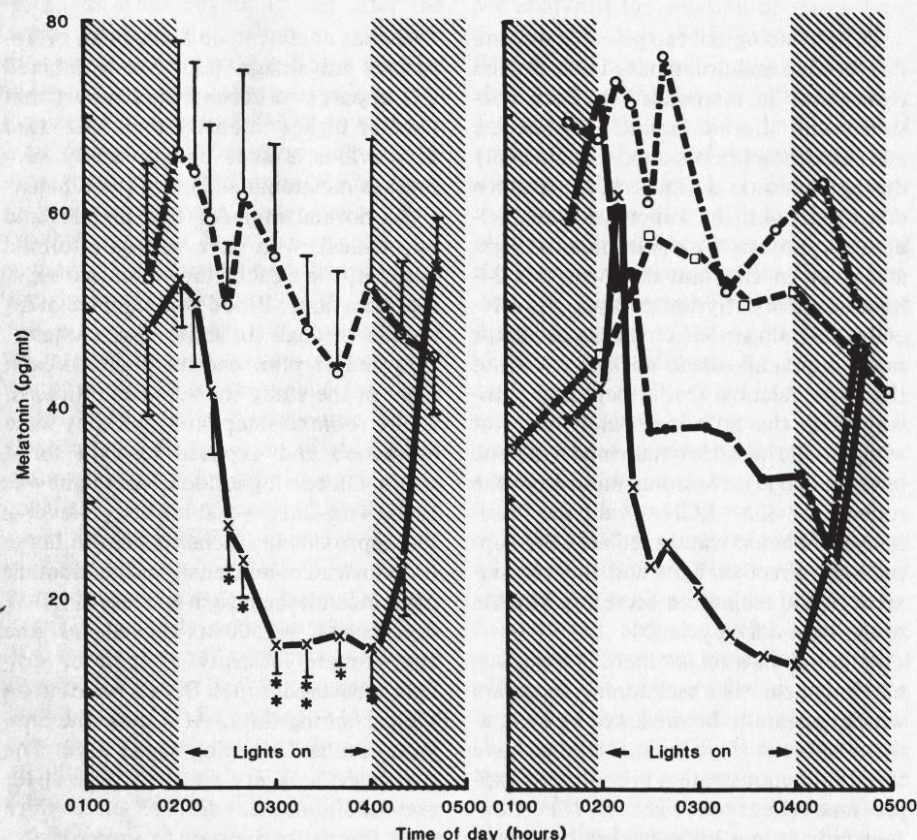


Fig. 1 (left). Effect of light on melatonin secretion. Each point represents the mean concentration of melatonin ($\pm$ standard error) for six subjects. A paired *t*-test, comparing exposure to 500 lux with exposure to 2500 lux, was performed for each data point. A two-way analysis of variance with repeated measures and the Newman-Keuls statistic for the comparison of means showed significant differences between 2:30 a.m. and 4 a.m. (*, $P < .05$; **, $P < .01$). Fig. 2 (right). Effect of different light intensities on melatonin secretion. The averaged values for two subjects are shown. Symbols: (○) 500 lux; (X) 2500 lux; (●) 1500 lux; and (□) asleep in the dark.

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 21. Some investigators did speculate that humans might require light of higher intensity (8, 9); some also proposed that "extrapineal sources of melatonin" could mask an effect of light on the pineal gland (9, 23). However, we demonstrated that significant amounts of melatonin could not be detected in the plasma of pinealectomized rats by GC-MS [A. J. Lewy, M. Tetsuo, S. P. Markey, F. K. Goodwin, I. J. Kopin, *J. Clin. Endocrinol. Metab.* 50, 204 (1980)]. Our results contradicted those of H. J. Lynch, Y. Ozaki, D. Shagal, and R. J. Wurtman [*Int. J. Biometeorol.* 19, 267 (1975)] and Y. Ozaki and H. J. Lynch [*Endocrinology* 99, 641 (1976)], who used bioassays or radioimmunoassays.
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Glucose Suppresses Basal Firing and Haloperidol-Induced Increases in the Firing Rate of Central Dopaminergic Neurons

Abstract. In the rat, doses of glucose sufficient to raise glucose concentrations in the blood to levels equivalent to those produced by a meal or stress suppress the firing of dopamine-containing neurons located within the substantia nigra. Glucose also prevents or reverses the increase in discharge rates of dopaminergic cells normally elicited by the antipsychotic agent haloperidol.

Central dopamine-mediated systems play an important role in maintaining motivated feeding behaviors especially in response to abrupt decreases in glucose use (1). We now report that glucose administration suppresses the firing of central dopaminergic neurons within the zona compacta of the substantia nigra (SNc). These findings are perhaps related to the broad influence of these neurons on motor, sensory, and cognitive functions (2).

Male albino Sprague-Dawley rats (175

to 350 g, Zivic-Miller) were housed two per cage and maintained on an alternating 12-hour light-dark cycle with free access to food and water. Animals were anesthetized with chloral hydrate (400 mg per kilogram of body weight) and mounted in a stereotaxic apparatus. A recording micropipette filled with 2M NaCl saturated with Fast Green dye (in vitro impedance, 2 to 10 megohms) was lowered into the region of the SNc [anterior, 1300 to 2400 μ m; lateral, 1300 to 2400 μ m (3)], and single unit activity was recorded (4). Dopaminergic neurons were located on the basis of previously described electrophysiological criteria (5). Briefly, these neurons have spontaneous firing rates of 1 to 9 Hz, often display a train of action potentials or "bursts" upon discharge, have biphasic waveforms (positive or negative) with amplitudes of 0.4 to 1.5 mV, and durations as long as 4 msec. All control cells (dopaminergic neurons tested with hypertonic saline, L-glucose, or D-fructose) also met the pharmacological criteria for mesencephalic dopaminergic cells (5). That is, their firing rates were slowed by the administration of a dopamine agonist (amphetamine) and increased by a dopa-

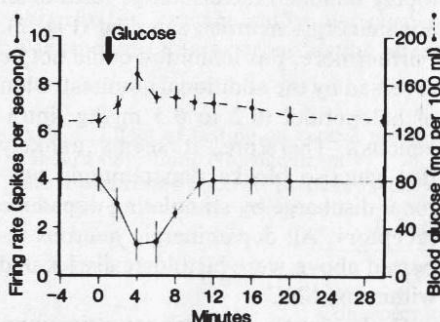


Fig. 1. Changes in the spontaneous activity of dopamine-containing neurons located within the SNc (mean $\pm$ standard error, $N = 6$) and blood glucose ($N = 8$) after the administration of D-glucose (15 mg/kg, intravenous).